Cancer and Pregnancy: Parallels in Growth, Invasion, and Immune Modulation and Implications for Cancer Therapeutic Agents

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Many proliferative, invasive, and immune tolerance mechanisms that support normal human pregnancy are also exploited by malignancies to establish a nutrient supply and evade or edit the host immune response. In addition to the shared capacity for invading through normal tissues, both cancer cells and cells of the developing placenta create a microenvironment supportive of both immunologic privilege and angiogenesis. Systemic alterations in immunity are also detectable, particularly with respect to a helper T cell type 2 polarization evident in advanced cancers and midtrimester pregnancy. This review summarizes the similarities between growth and immune privilege in cancer and pregnancy and identifies areas for further investigation. Our PubMed search strategy included combinations of terms such as *immune tolerance*, *pregnancy*, *cancer*, *cytokines*, *angiogenesis*, and *invasion*. We did not place any restrictions on publication dates. The knowledge gained from analyzing similarities and differences between the physiologic state of pregnancy and the pathologic state of cancer could lead to identification of new potential targets for cancer therapeutic agents.

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CTL = $CD8^+$ T cytotoxic lymphocyte; DC = dendritic cell; EVT = extravillous trophoblast; HLA = human leukocyte antigen; IL = interleukin; NK = natural killer; T_H1 = helper T cell type 1; T_H2 = helper T cell type 2; T_{reg} = regulatory T cell; uNK = uterine NK

A substantial body of literature exists describing the mechanisms cancer cells use to escape apoptosis and migrate through normal structures while evading a host immune response. What is not well known, however, is how these complex and interrelated mechanisms are orchestrated, starting with modulation of the immune response within the tumor microenvironment and ending with migration and proliferation of cancer cells at distant sites. One potential model to further study how a single malignant cell could proliferate and then metastasize undetected within a host is that of normal human pregnancy, in which the developing placenta invades the uterus and a semiallogeneic fetus escapes rejection from the maternal immune system.[1] A multitude of immunomodulatory properties of the fetomaternal interface (placenta) have evolved to allow the survival of the immunologically distinct fetus to parturition without an attack from the maternal immune system. The similarities between the mechanisms involved in fetomaternal and tumor-associated immunologic tolerance are intriguing and suggest a common pattern; however, neither system of immune evasion is perfect. A clear example of placental failure to protect the fetus against maternal immunity is that of Rh incompatibility. In multiparous women sensitized against fetal Rh antigens, re-exposure to fetal Rh antigens with subsequent pregnancy may lead to hemolytic disease of the newborn and fetal death.[2] Such imperfections of shared mechanisms of immune tolerance between pregnancy and cancer suggest that cancer rejection via immunologic means may be possible, even considering the myriad mechanisms extending immunologic privilege to the fetus as well as cancer cells.

This review summarizes the parallels in proliferation, invasion, and immune privilege between cancer and pregnancy by first detailing shared characteristics of fetal-derived trophoblast cells of the placenta and tumor cells. It then describes the similarities between tolerogenic systems within the tumor microenvironment and the fetomaternal interface. Finally, it provides an overview of the evidence for systemic immune modulation in cancer and pregnancy and suggests the implications of these similarities in designing an integrated approach to cancer therapy. Our PubMed search strategy included combinations of terms such as *immune tolerance*, *pregnancy*, *cancer*, *cytokines*, *angiogenesis*, and *invasion*. We also searched for articles on cellular subsets, including natural killer (NK) cells, dendritic cells (DCs), regulatory T cells (T_{reg}), and other lymphocyte populations with respect to their presence and function in pregnancy and cancer. We did not place any restrictions on publication dates. A better understanding of how the maternal immune system is altered during the normal processes of implantation, gestation, and labor may translate into individualized, novel therapies aimed at restoring immune competency in patients with advanced malignancies.

SHARED CHARACTERISTICS OF TROPHOBLAST CELLS AND TUMOR CELLS

Five days after fertilization, the human zygote forms into a structure consisting of 2 primary cell lines: the inner cell

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A glossary of genetics terminology appears at the end of this article.

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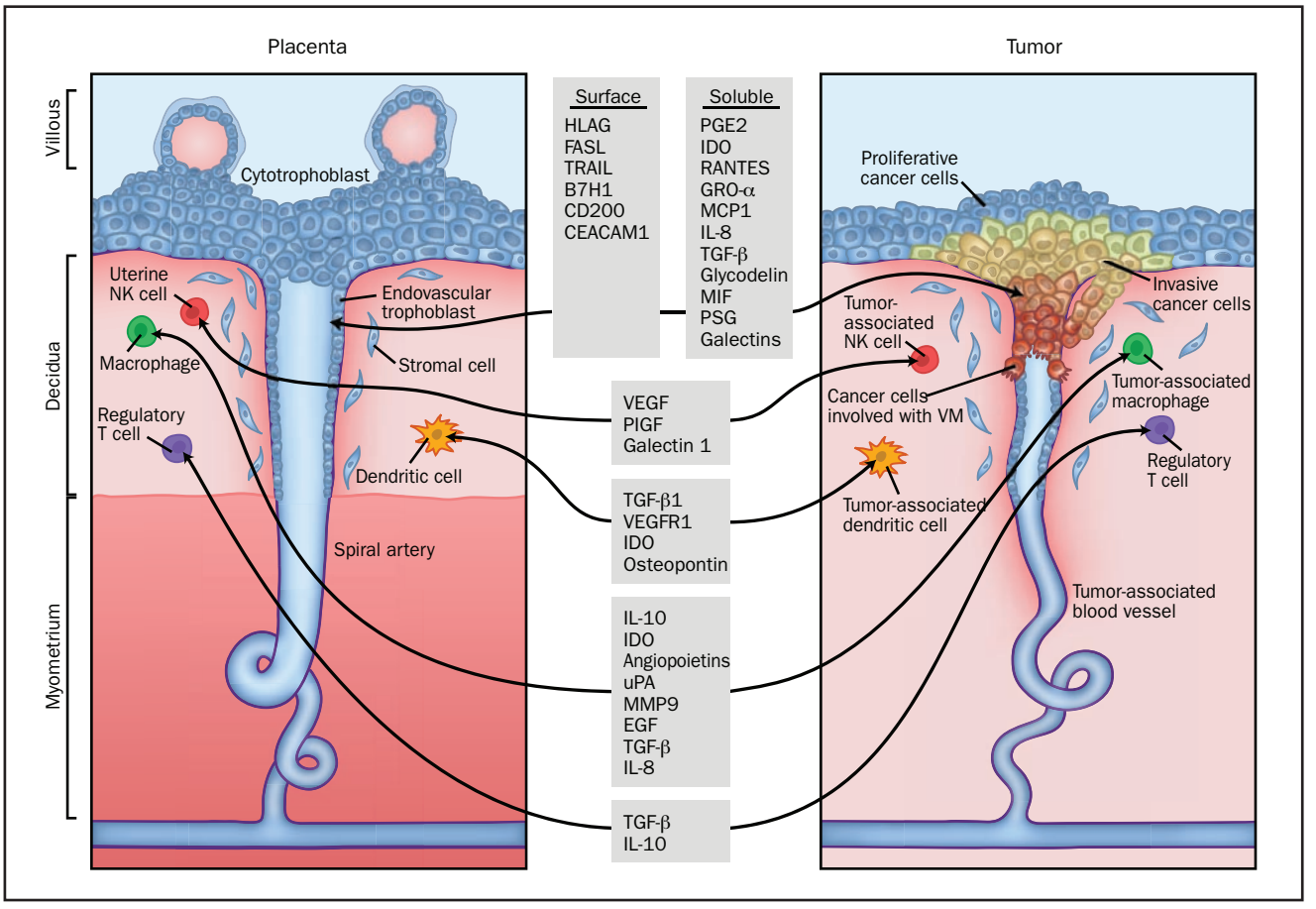

FIGURE. Similarities between the fetomaternal interface and tumor microenvironment. For expansion of all gene symbols, see Glossary of Genetics Terminology at the end of the article. HLA = human leukocyte antigen; IL = interleukin; VM = vasculogenic mimicry.

mass (or embryoblast) and the trophoblast.[3] Trophoblast cells constitute the outer layer of the blastocyst, rapidly proliferating and invading the maternal endometrial decidua around day 7. A monolayer of cytotrophoblast cells surrounds the embryonic disc as the embryo completely embeds beneath the uterine decidua. By day 9, cytotrophoblast cells have differentiated into 2 distinct cell types: the syncytiotrophoblast and the extravillous trophoblast (EVT). The multinucleated syncytiotrophoblast cells form the external layer and are terminally differentiated. These cells are involved in fetomaternal nutrient exchanges and endocrine functions (such as β-human chorionic gonadotropic production). In contrast, EVT cells have a proliferative and invasive phenotype, migrating through the syncytiotrophoblast into the uterine wall to anchor the placenta beginning around day 14 after implantation.[4] These EVT cells display a phenotype strikingly similar to cancer cells with their capacity for proliferation, migration, and establishment of a blood supply, making them a compelling model for oncologic comparison (Figure). This review highlights several shared characteristics of trophoblast and tumor cells and discusses them in the context of existing or developmental targeted cancer therapeutics (Table 1).

PROLIFERATION

Like tumor cells, trophoblast cells have a very high proliferative capacity and exhibit molecular characteristics found in rapidly dividing cancer cells.[54] For example, increased telomerase activity, typically not observed to a substantial degree in normal somatic cells, is detectable in 85% of human cancers.[55] In fact, the intracellular concentration of telomerase is exponentially related to the proliferative capacity of a cell.[56] In human pregnancy, telomerase activity is highest during the first trimester and decreases with maturation of the placenta.[57] Survivin, a protein that promotes proliferation and inhibits apoptosis, is overexpressed in many cancers[58] and is also up-regulated by trophoblast cells.[59] Inhibition of survivin by knockdown with small interfering RNA leads to a marked decrease in proliferation in

TABLE 1. **Tumorlike Attributes of the Human Trophoblast Cells and a Selection of Representative Targeted Cancer Therapeutic Strategies in Use or Development**[a]

Shared trophoblast-tumor attribute	Mechanism	Targeted therapeutic strategy	Drug/compound name[b]
Self-sufficiency in growth signals	Activation of MAPK pathway	Inhibition of RAS-RAF-MEK-ERK signaling	Sorafenib; ARRY-142886; PLX-4032; XL281; RAF265; PD0325901[5]
	Activation of PI3K-AKT pathway	Inhibition of RAS-PI3K-AKT-MTOR signaling	Quercitin, XL147, and XL765; GDC-0941; BEZ235; PX-866[6]; sirolimus; everolimus; temsirolimus
	FAK activation	FAK inhibition	TAE226[7]; dasatinib
	HGF autocrine loop	HGF or C-MET inhibition	OA-5D5[8]; AMG-102[9]; SGX-523; PF-0234106; XL880
	EGF autocrine loop	EGF or EGFR inhibition	Erlotinib; cetuximab; panitumumab; XL647
	IGF autocrine loop	IGF or IGFR inhibition	AEW541[10]
	CSF autocrine loop	CSF1 or CSF1R inhibition	GW2580[11]; CYC10268[12]
	PDGF autocrine loop	PDGF or PDGFR inhibition	AZD2171; pazopanib; sorafenib; sunitinib; E7080; ZD6474; AG-013736
	VEGF autocrine loop	VEGF or VEGFR inhibition	Bevacizumab; RAF265; BMS-690514
Insensitivity to antigrowth signals	TGF-β pathway activation	TGF-β2 blockade	AP 12009[13]; LY-2157299[14]
	CDK	CDK inhibition	SNS-032[15]; AT7519[16]; flavopiridol
	SMAD	ALK inhibition leading to decreased SMAD phosphorylation	A 83-01[17]
Evasion of apoptosis	IGF1R signaling	IGF1R blockade	Concept reviewed by Werhova and Haluska[18]; R1507; CP-751,871[19,20]
	PDGFR signaling	PDGFR blockade	Imatinib; sorafenib; sunitinib; E7080; ZD6474; AG-013736; pazopanib
	BCL2	BCL2 inhibition	Oblimersen
	Survivin	Survivin inhibition	YM-155; terameprocol
	XIAP	XIAP antisense	AEG35156
	Endoreduplication	Maintain p53 integrity; Aurora kinase inhibition; induction of p21 (waf1/cip1)	Nutlin-3a (promotes endoreduplication)[21]; VX-680[22]; theaflavins[23]
Limitless replicative potential	Telomerase	Telomerase inhibition	GRN163L; RHPS4
	HGF–C-MET signaling	MET inhibition	PF-0234106
Sustained angiogenesis	VEGFR signaling	VEGF inhibition	Bevacizumab; sorafenib; sunitinib; E7080; ZD6474; AG-013736; pazopanib; IMC-1121B; AZD2171; CHIR-265; ABT-510; BMS-690514; XL880; aflibercept
	HIF-1α	HIF-1α inhibition	PX-478
	PGF	PGF inhibition	TB-403[24]
	FGF	FGF inhibition	PI-88
Tissue invasion	Integrins	α2 integrin inhibition; αv integrin inhibition; αvβ3 + αvβ5 integrin inhibition; αvβ3 integrin inhibition	E 7820; CNTO 95; cilengitide; abergrin (MEDI 522)
	MMPs	Down-regulation of MMPs	Curcumin[25]; Saponins[26]
	Wnt signaling	Cyclooxygenase-2 inhibition	Celecoxib[27]
	HSP27	3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibition	Lipophilic statin medications: atorvastatin, simvastatin, lovastatin, or fluvastatin[28]
Immune evasion	Decreased HLA class I expression	Increased HLA class I expression	Gamma irradiation[29]; samarium-153-ethylenediaminetetramethylenephosphonate[30]; DNA-demethylating agent 5-aza-2′-deoxycytidine[31]
	Nonclassical HLAG expression	Neutralization of soluble HLAG or reduced gene transcription of HLAG	None yet developed, but 5-aza-2′-deoxycytidine increases HLAG in leukemia cell lines with unknown clinical immunomodulatory impact[32]
	PGE2	Decreased PGE2 synthesis	Celecoxib[33]
	Complement regulatory proteins	Neutralization of miniantibodies to CD55 and CD59	MB55 and MB59 tested in mouse models only at time of writing of this manuscript[34]
	IDO	Decreased IDO expression, IDO blockade	Celecoxib,[35] 1-methyl D-tryptophan[36]
	CD44 expression (also soluble)	CD44 ligation	Anti-CD44 monoclonal antibodies[37]
	MUC1	MUC1 radioimmunotherapy	Radioimmunotherapy with MUC1 monoclonal antibody[38,39]
	Neuropilin 1 and 2	Neuropilin receptor blockade	None yet available, but concept reviewed by Mac Gabhann and Popel[40]
	B7H1	B7H1 blockade	None yet available, but concept reviewed by Thompson et al[41]

(Continued on next page)

TABLE 1. **Continued**[a]

Shared trophoblast-tumor attribute	Mechanism	Targeted therapeutic strategy	Drug/compound name[b]
Immune evasion (continued)	FASL	Recombinant FASL	APO010[42]
	CCL5	CCL5 vaccine adjuvant	Engineered CCL5 superagonist[43]
	TRAILR	TRAILR2 agonist	Lexatumumab
	TIM3	TIM3 blockade	None yet available, but concept reviewed by Anderson[44]
	TLR	Synthetic TLR agonists	Ampligen (TLR3 agonist)[45]; imiquimod (TLR7 agonist)[46]
	Galectins	Galectin inhibition	GCS-100 (Galectin 3 antagonist)[47]; thiodigalactoside ester derivatives[48]
	CD200	CD200 antibody	ALXN6000[49]
	SDF1 (also known as CXCL12)	CXCR4 (CXCL12 receptor) antagonism	Plerixafor[50]; CTCE-9908[51]
	Osteopontin	Down-regulation of osteopontin expression	Small interfering RNA therapy[52]

[a] HLA = human leukocyte antigen. For expansion of all gene symbols, see Glossary of Genetics Terminology at the end of the article.
[b] Data regarding drug compounds are from *Mayo Clin Proc*,[53] unless a citation is given to indicate otherwise.

trophoblast cell lines.[60] A similar decrease in proliferation is seen with survivin in small interfering RNA treatment of prostate,[61] glioma,[62] non-Hodgkin lymphoma,[63] cervical cancer cells, and breast cancer cells.[64] Both survivin and telomerase levels are dramatically higher in hydatidiform moles than in normal placentas, providing insight into the potential involvement of these 2 different mechanisms in neoplastic transformation.[59]

Another pathway supportive of both trophoblast and cancer cell proliferation is the IGF pathway (for expansion of all gene symbols, see Glossary of Genetics Terminology at the end of the article). By binding to the IGF1R on cytotrophoblast cells, IGF stimulates proliferation through the MAPK pathway and survival via activation of the PI3K pathway.[65] Normally, levels of IGF are tightly regulated by IGF-binding proteins and protease pregnancy-associated plasma protein A, a binding protein.[66] Loss of binding protein regulation may contribute to the malignant phenotype.[67] In cancer cells, the IGF1R pathway is not only mitogenic and antiapoptotic but is involved in protecting cancer cells from damaging effects of chemotherapy and radiation, potentially as a result of its effects on downstream signaling pathways.[68] Additionally, the fetal form of the insulin receptor IR-A, which is highly expressed in fetal tissues and responsive to IGF2, is also a member of the IGF-signaling system.[69] In many cancers, including those of the breast and ovary, dysregulation of this fetal form of the insulin receptor becomes the predominant isoform leading to IGF2-stimulated proliferation and survival.[70,71]

INVASION

The sine qua non of both a successful pregnancy and the growth of cancer is the establishment of a blood and nutrient supply, and invasion through normal tissues is required for this process. However, whereas cancer cells spread throughout the host and then engage in local proliferation, trophoblasts follow an organized pattern of differentiation from proliferation to invasion without distant metastasis.[72] Some of the molecular switches involved in this differentiation pattern and their relevance for cancer therapeutic agents are discussed in the sections that follow.

As EVT cells migrate down the cytotrophoblast cell columns into the maternal decidua (Figure), they encircle and erode into the maternal spiral arteries and differentiate from a proliferative phenotype into an invasive phenotype.[73] This differentiation occurs at about 10 to 12 weeks of gestation and is associated with opening of the intervillous space and exposure to maternal blood. Many parallels can be observed between invasive EVT cells and cancer cells. Some of these similarities are highlighted in the sections to follow; for a more in-depth discussion, readers should refer to excellent reviews by Soundararajan and Rao[74] and Ferretti et al.[75]

Requirements for cellular invasion include changes in cell adhesion molecules, secretion of proteases, and availability of growth factors. An example of a cellular program used by both cancer cells[76] and trophoblast cells[77] to promote invasion is epithelial-mesenchymal transition, which results in loss of cell-to-cell contact inhibition. Associated with this program are changes in integrin expression and loss of E cadherin, allowing loss of polarity and enhanced motility.[78,79] Both trophoblast and cancer cells secrete proteases to degrade extracellular matrix proteins required for dispersal through tissues. The cytoplasm of migratory EVT cells express HSP27, which is correlated with MMP2 activity.[80] Basal HSP27 levels are unusually high in cancer cells, protecting them from apoptotic stimuli,[81] and are associated with metastatic potential.[82] Finally, growth factors such as epidermal growth factor stimulate motility of EVT cells through phosphorylation of p42 and p44 MAPKs and the PI3K-dependent proteins, AKT and p38.[83] Epidermal growth factor is associated with tumor cell invasiveness through expression of MMPs.[84]

Switches involved in triggering trophoblast and cancer cell molecular programs for invasion are not completely understood. The Wnt pathway, a system highly conserved across species involved in cellular proliferation and motility, has recently been implicated in switching trophoblast cells from a proliferative to an invasive phenotype.[85] Activation of the Wnt pathway is aberrant in many cancers, resulting in escape of β-catenin from proteosomal degradation, with subsequent β-catenin translocation into the cell nucleus and activation of multiple target genes.[86] Although direct activation of β-catenin alone has shown no effect on motility of EVT cells, inhibition of the Wnt –β-catenin pathway can block blastocyst implantation.[87] In EVT cells, activation of PAR1 (also known as the thrombin receptor) also stabilizes β-catenin and is associated with a proliferative and invasive capacity, whereas application of PAR1-silencing RNA inhibits EVT invasion.[88] Consistent with the need for tight regulation of invasive trophoblast cells, PAR1 is expressed in EVT cells between the 7th and 10th gestational week but is abruptly shut off by the 12th week.[89] Constitutive increased expression of PAR1 can be seen in cancer cells, especially in cells lacking normal p53 activity.[90] In vitro assays have shown PAR1 antagonism to inhibit MMP1-induced endothelial cell activation in tumor–endothelial cell communication.[91] Whether this system could successfully be targeted for cancer therapy is under investigation. Other signal transduction pathways common in both trophoblast and cancer cell invasion include the JAK-STAT pathway,[92] FAKs, G proteins, Rho-associated kinase, MAPKs, PI3K, and SMAD family proteins.[73] All of these pathways represent areas of current anticancer therapeutic development.

As EVTs acquire an invasive phenotype during placental development, they become polyploid (4N-8N) by switching from mitotic division to endoreduplication,[93] a process in which G2 or M phase (4N) cells replicate DNA without undergoing mitosis. In trophoblast cell lines, polyploid trophoblast giant cells are relatively resistant to the DNA-damaging effects of radiation,[94] illustrating a mechanism by which survival is promoted in invasive trophoblast cells. This process can also be observed in cancer cells treated with DNA-damaging agents. Endoreduplication can be induced in tumor cells on exposure to genotoxic agents such as paclitaxel[95] and cisplatin; a nonproliferative, senescent state in a small population of cells is induced in the latter case. The polyploid tumor cells can undergo depolyploidization to form diploid, cisplatin-resistant escape cells.[96] In cells with an impaired p53 system, treatment with the Aurora kinase inhibitor VX-680 leads to endoreduplication followed by apoptosis.[22] However, in 2 wild-type p53 cancer cell lines, stabilization of p53 by Nutlin-3a, an inhibitor of the p53-binding protein MDM2, leads to initial endoreduplication followed by the emergence of stable radiation- and cisplatin-resistant tetraploid clones.[21] A better understanding of the EVT endoreduplication process may lead to the development of targeted drugs to maintain tumor cell chemotherapeutic sensitivity.

VASCULOGENIC MIMICRY

As trophoblasts invade maternal spiral arteries, they further differentiate to display a vascular phenotype in a process termed *vasculogenic mimicry*, in which cells other than endothelial cells form vascular structures.[97] Vasculogenic mimicry can also be observed in aggressive cancers, and the genes and signaling pathways involved with the process of vasculogenic mimicry may be shared between EVT and cancer cells.[98] For example, the matrix glycoprotein–binding galectin 3 is highly expressed in EVT cells.[99] Galectin-3 also appears to be a key factor in the development of an endothelial phenotype and the tube formation well described in aggressive melanomas.[100] Galectin inhibitors are in preclinical testing as cancer therapeutic agents.[101] Mig-7 was found in circulating tumor cells and tumor tissue (regardless of tissue of origin) from more than 200 patients with cancer; notably, it was absent from healthy controls.[102] Mig-7 expression is associated with invasion and vasculogenic mimicry in cancer cells and also has recently been demonstrated in invasive embryonic cytotrophoblasts, peaking when EVT cells invade maternal decidua and remodel the vasculature during early placental development.[103] This finding represents the only known expression of Mig-7 in noncancerous cells. Cancers with an endothelial phenotype have not been shown to be responsive to antiangiogenic therapies.[104] Because cancer therapy aimed at proliferating cells is less likely to be effective in invading cells,[105] galactin-3, Mig-7, and other pathways involved in vasculogenic mimicry may also be important targets for cancer therapy.

ANGIOGENESIS

Molecular circuits involved in neoangiogenesis separate from vasculogenic mimicry are also likely shared between EVT and tumor cells. Angiopoietins and VEGF family members are extremely important in both spiral artery remodeling in placentation[106] and the growth of many tumor types.[107] Inhibition of VEGF has become an important therapeutic strategy in many cancers, although resistance can develop,[108] resulting from the induction of an angiogenic rescue program characterized by the up-regulation of multiple angiogenic genes in hypoxic tumor cells and supporting stroma.[109,110] Another member of the VEGF family, PGF, is a part of the VEGF blockade–associated rescue program that

is involved in the response to pathologic conditions, such as wounds, ischemia, inflammation, or cancer.[111] Both VEGF and PGF are highly expressed in trophoblast cells.[112] It is interesting that serum levels of PGF increase after treatment of patients with cancer with the anti-VEGF monoclonal antibody bevacizumab.[113] Preclinical studies indicate that PGF blockade reduces neoangiogenesis and lymphangiogenesis, hampers recruitment of intratumoral macrophages, and is not associated with the typical anti-VEGF adverse effects (thrombosis, hypertension, proteinuria, and microvascular pruning) in healthy mice.[110]

Also important for angiogenesis is the oxygen-sensitive MTOR pathway.[114] Central to controlling trophoblast cell proliferation in response to nutrients and growth factors,[115] MTOR is expressed on the transporting epithelium of intact human placenta.[116] It is downstream of the PI3K/AKT pathway; controls cell cycle progression and cell size and mass; is involved in angiogenesis via the VEGF, IGF, and HIF-1α–signaling pathways; and is constitutively activated in many malignancies.[114,117] The MTOR inhibitor everolimus has antiangiogenic properties.[118] A better understanding of the PI3K/AKT/MTOR pathway and other molecular circuits used by trophoblast cells in proliferation, invasion, and endothelial interactions may lead to the development of targeted therapies for cancer.[75] Overall, we are in our infancy of understanding the complexity, redundancy, and interrelatedness of these molecular pathways in both placentation and neoplasia.

IMMUNOLOGIC PROPERTIES OF THE FETOMATERNAL INTERFACE AND TUMOR MICROENVIRONMENT

In addition to sharing many proliferative and invasive features, the cells of the trophoblast, like cancer cells, actively modulate the host immune response to develop and sustain a nutrient supply. Historically, the placenta was considered an inert, mechanical barrier protecting the semiallogeneic fetus from maternal immunologic attack.[119] Current evidence, however, supports just the opposite—many maternal and placental immunomodulatory factors are required for adequate placental invasion. Around 40% of decidual cells are cells of the innate immune system (eg, NK cells, macrophages, and DCs), a substantial proportion considering that the uterus is a nonlymphoid organ.[120] Likewise, although cancer previously has been considered immunologically invisible to the host, many recent studies support the notion that cancer cells actively engage immune cells; for example, the presence of tumor-infiltrating lymphocytes has been well described in the literature.[121] The main components of the maternal immune response at the fetomaternal interface and the similarities to the tumor microenvironment are discussed in the sections that follow.

The most abundant immune cell present at the fetomaternal interface is the uterine NK (uNK) cell, which constitutes approximately 70% of all immune cells found in this tissue.[122] Uterine NK cells are thought to be recruited from peripheral blood when interleukin (IL)-15 is secreted by endometrial stromal cells.[123] They are distinct from peripheral blood NK cells in that they do not express CD16, the FcRγIIIA receptor required for antibody-dependent cell-mediated cytotoxicity.[120] The mechanisms associated with this loss of CD16 are unclear but may be related to high levels of TGF-β within the microenvironment.[124] Also, in contrast to peripheral blood NK cells, uNK cells are more immunomodulatory than cytotoxic, secreting galectin 1 to induce tolerogenic DCs[125] as well as angiogenic factors VEGF and PGF that are important for decidual remodeling.[126] An improper balance of cytotoxic to regulatory NK cells could contribute to recurrent miscarriage and pre-eclampsia.[127] Expression of IL-15 and NK cell infiltration have been reported in many different malignancies,[128] including renal cell carcinoma,[129] with variable prognostic implications. Recently, tumor-infiltrating CD16-NK cells have also been characterized and appear to behave similarly to uNK cells with respect to cytokine production and reduced cytotoxic activity.[130] A closer look at factors that determine the balance of killer and regulatory NK cells during pregnancy may help identify mechanisms that shift immunity toward NK cytotoxic activity in patients with cancer.

Also infiltrating the decidua, albeit in smaller numbers than uNK cells, are macrophages, T_{reg}, and DCs. Macrophages phagocytose apoptotic EVT cells and secrete IL-10 and IDO, contributing to the tolerogenic T_H2 milieu.[131] Gene expression profiling of decidual macrophages supports an immunosuppressive/anti-inflammatory phenotype with higher expression of *CCL18*, *IGF1*, *IDO*, neuropilin 1, and other genes associated with M2-polarized macrophages.[132] Tumor-associated macrophages can be both inflammatory and immunosuppressive, and T_H1/T_H2 polarization is effected through the activation of NF-κB (also known as NFKB1).[133] In fact, in vitro studies suggest that tumor-associated macrophages may be re-educated to display a classically activated rather than an M2 phenotype by inhibition of inhibitory kappa B kinase β, the major activator of NF-κB.[134]

Regulatory T cells are additional important mediators of tolerance in both pregnancy and cancer. Immunophenotypically, these cells express surface CD4, CD25, and FOXP3, and they expand in both decidua[135] and peripheral blood[136] during normal pregnancies. This expansion is antigen-specific and is induced by paternal/fetal alloantigens[137] and not simply by hormonal changes in pregnancy.[138] A decrease in this lymphocyte subset is associated with spontane-

ous abortion[139] and pre-eclampsia.[140] Regulatory T cells are also expanded in cancer and are implicated in impaired antitumor immunity,[141] suppression of effector T lymphocyte proliferation,[142] and increased tumor blood vessel density,[143] suggesting an important link between immunity and angiogenesis. Regulatory T cells in patients with cancer also recognize tumor-specific antigens and proliferate in response to antigenic stimulation.[144] Targeting the T_{reg} population to boost antitumor immunity is under investigation with agents such as denileukin diftitox (IL2/diphtheria fusion protein) or LMB-2 (Fv fragment of CD25 antibody/*Pseudomonas* endotoxin A fusion protein) and CTLA-4 inhibitors.[145,146] Some of the benefit of cytotoxic chemotherapy may be derived from concomitant impairment of the immunosuppressive T_{reg} proliferation driven by the cancer.[147]

Antigen-presenting $CD83^+$ DCs are involved in the maintenance of the T_H2-predominant state in decidual tissues,[148] as well as at other mucosal surfaces.[149] However, the role of the DC is likely more complex than antigen presentation and secretion of immunosuppressive cytokines. Ablation of uterine DCs leads to decidualization failure and embryo resorption in mice; this occurs even with syngeneic pregnancy in mice in which alloantigens are absent.[150] Dendritic cells also represent another link between immunity and angiogenesis, secreting soluble FLT1 (also known as VEGFR1) and TGF-β1 required for endothelial cell survival and vascular maturation. In the absence of DCs, angiogenesis is severely impaired. In cancer, DCs also play a role that is more than immunoregulatory through their production of potent angiogenic growth factors. Moreover, cancer cells can secrete substances that suppress maturation of DCs, including VEGF, TGF-β, hepatocyte growth factor, and osteopontin, thereby maintaining a proangiogenic, immature DC phenotype.[151]

Expression of certain cell surface molecules on both trophoblast and cancer cells can also confer immunologic protection. Among the most important of these molecules is the nonpolymorphic, highly conserved class I human leukocyte antigen (HLA) molecules such as HLAG[152]; in contrast, the highly diverse classical HLA class I proteins A, B, and C are essential in cell-mediated immune responses. In fact, in trophoblast cells, interferon-γ fails to stimulate classical HLA class I expression.[153] A similar property of down-regulated or absent classical HLA class I expression can cloak cancer cells from the host's immune system.[154] Cancer treatment modalities including gamma irradiation,[29] radiopharmaceutical samarium-153-ethylenediaminetetramethylenephosphonate,[30] and chemotherapeutic agents such as 5-fluorouracil[155] and hypomethylating agents[156] increase HLA class I expression.

Expression of HLAG on trophoblast cells and cancer cells has important immunomodulatory effects. In the placenta, HLAG expression is most evident on EVTs at the fetomaternal interface, with lower expression at the proliferative area of the villous column and increased expression with invasive, interstitial, and endovascular EVT cells.[157] On the basis of sequence homologies, *HLAG* has been proposed as the ancestral MHC class I gene and has only a few known sequence variations in humans, in sharp contrast to the profound allelic diversity (measured in the hundreds of allelic variants) of classical MHC class I genes.[158] Human leukocyte antigen-G interacts with NK cells via inhibitory receptors, such as CD94/NKG2A, ILT2, and killer cell immunoglobulin-like receptor KIR2DL4.[120] The role of HLAG is to suppress cytolytic killing by both NK and cytotoxic T cells, induce apoptosis of immune cells, regulate cytokine production in blood mononuclear cells, and reduce stimulatory capacity and impair maturation of DCs (reviewed in Hunt et al[159]). Within the tumor microenvironment, the generation of $HLAG^+$–suppressive NK cells occurs by trogocytosis (ie, the rapid cell-to-cell contact-dependent transfer of membranes and associated molecules from one cell to another), leading to the inhibition of other $HLAG^+$ (cross-inhibition) or $HLAG^-$ NK cells through HLAG and ILT2 cross-linking.[160] Expression of HLAG is associated with a poor prognosis in patients with lymphoproliferative disorders,[161] melanoma,[162] mesothelioma,[163] breast carcinoma,[163] ovarian carcinoma,[164] renal cell carcinoma,[165] squamous esophageal cancer,[166] gastric carcinoma,[167] cervical cancer,[168] non–small cell lung cancer,[169] bladder cancer,[170] prostate cancer,[171] endometrial cancer,[172] colorectal cancer,[173] and myeloid malignancies, including acute myeloid leukemia.[174,175] However, relatively little is known about the regulation of the expression of this important immunomodulatory molecule.[174] Regulation of HLAG expression may be at the epigenetic level, with transcription of HLAG being detectable in acute myeloid leukemia cell lines after treatment with 5-aza-2′-deoxycytidine.[32] Some preliminary evidence also supports a micro-RNA regulatory mechanism.[176] Clearly, HLAG represents an attractive target for immune-based cancer therapies given its preferential expression in many malignancies as well as limited expression in normal tissues.[177] Targeting HLAG with a peptide-based vaccine strategy to develop a cytotoxic T-cell response against tumor cells bearing the molecule has proved feasible,[178] although much work remains before other methods of HLAG inhibition could lead to restoration of antitumor immunity.

Other cell surface tolerance signals common between trophoblasts and cancer cells include CD200 (OX-2) and CEACAM-1. Trophoblast cells expressing CD200 can inhibit $CD8^+$ T cytotoxic lymphocyte (CTL) generation and shift the cytokine balance toward T_H2 in vitro.[179] Expression of CD200 is a negative prognostic factor in patients with multiple myeloma[180] and acute myeloid leukemia,[181] and

it has been shown to down-regulate T_H1 cytokines in vitro in solid tumors, including melanomas, ovarian carcinomas, and renal cell carcinomas.[182] As a potential cancer stem cell marker, CD200 may be a promising target for these cells that survive conventional chemotherapy.[183] CEACAM-1 (CD66a), expressed on both trophoblasts and IL-2–activated decidual leukocytes, plays a role in inhibiting NK-mediated cytolysis.[184] Colocalization of osteopontin on EVT cells is associated with an invasive phenotype important for successful placentation.[185] CEACAM-1 expression in cancer is associated with increased angiogenesis in non–small cell lung cancer[186]; in melanoma, it has been shown to be predictive of the development of metastatic disease.[187] Expression of other immunomodulatory molecules, including components of the extrinsic apoptotic pathway such as FAS, TNF superfamily receptors,[188] TRAIL,[189] and B7 family members such as B7H1 (or programmed death ligand 1, PDL-1),[190] is also common between trophoblast and cancer cells (Table 1).

Chemokines and cytokines also play a role in promoting a tolerogenic environment in placentation and the tumor microenvironment. Implantation of the blastocyst occurs in a T_H1-predominant (inflammatory) milieu, but the fetomaternal interface must transition to a T_H2-polarized (immunologically tolerant) state for pregnancy to continue (for an excellent review, refer to van Mourik et al[191]). However, before implantation can occur, the endometrial lining must be receptive in the so-called window of implantation, in which many immunomodulatory genes are up-regulated monthly during the midsecretory phase of the menstrual cycle.[191] Under the influence of progesterone, the endometrial epithelium up-regulates decay-accelerating factor and osteoponin expression, and the endometrial stroma increases IL-15 expression.[192,193] Expression of complement regulatory proteins (eg, decay-accelerating factor) is a well-established immunomodulatory mechanism used by many cancers to escape complement-mediated cell death and evade an immune response by inhibiting T-cell proliferation.[194] Osteopontin has T_H1 cytokine functions and is chemotactic for macrophages, T cells, and DCs, the last of which it induces to secrete IL-12 and tumor necrosis factor α (TNF-α).[195,196] Osteopontin is overexpressed in many cancers and is associated with metastatic potential.[197] Additionally, tissues that physiologically express high levels of osteopontin, such as bone, lung, and liver, may create a receptive microenvironment for metastasis via interaction with osteopontin receptor CD44 on the surface of cancer cells.[198]

RANTES (CCL5) is a chemokine produced by trophoblasts that may play a role in apoptosis of potentially harmful maternal $CD3^+$ cells.[199] Melanoma cells can induce tumor-infiltrating lymphocytes to secrete RANTES and subsequently undergo apoptosis as another mechanism to evade an immune response.[200] Trophoblast cells also secrete chemoattractant cytokines, such as GRO-α, MCP1, and IL-8, to actively recruit the $CD14^+$ monocytes to the fetomaternal interface.[201] GRO-α is an oncogenic and angiogenic cytokine driven by RAS, which is inappropriately activated in most cancers.[202] Capable of inducing vascular permeability along with mononuclear cell recruitment, MCP1 is associated with angiogenesis and malignant pleural effusions.[203] Inhibition of MCP1 can lead to reduced malignant angiogenesis and recruitment of tumor-associated macrophages in a mouse model of melanoma.[204] Finally, the IL-8 pathway is well known to be a central immune and angiogenic factor within the tumor microenvironment and is important in stress-induced chemotherapeutic resistance.[205]

A tryptophan-catabolizing enzyme, IDO is important in promoting tolerance by inhibiting proliferation of lymphocytes both at the fetomaternal interface[206] and tumor microenvironment.[207] Tryptophan levels have been observed to decrease in pregnancy with a return to normal, nonpregnant levels in the puerperium,[208] possibly a result of tryptophan degradation by IDO-expressing trophoblast cells. Expression of HLAG on DCs can be induced by IDO, indicating potential cooperation in immune suppression between these 2 molecules.[209] Tumor-derived PGE2 secretion can increase IDO expression in local DCs.[210] Antigen-expressing cells and IDO-expressing tumor cells might also contribute to local immunosuppression in tumor-draining lymph nodes.[211] Pharmacologic inhibitors of IDO are under development and in early-stage clinical trials as anticancer agents.[207] Induction of IDO can also be blocked in vitro by cyclooxygenase 2 inhibitors.[212] When murine breast cancer vaccine recipients received the oral cyclooxygenase 2 inhibitor celecoxib, an increase in tumor-specific CTLs was observed.[35]

Trophoblast invasion and spiral artery remodeling are tightly controlled processes, likely kept in check both by molecular programming of trophoblast cells and by paracrine immune factors.[213] We have much to gain in terms of developing novel immunologic interventions for our patients with cancer by closely examining both the similarities and differences of the intimate cross-talk that occurs within the tumor and placental microenvironments.

EVIDENCE FOR SYSTEMIC IMMUNE MODULATION

Similar to the increasing antigenic burden of progressive cancer,[214] fetal DNA can be found circulating in maternal blood by the second trimester in the height of the tolerogenic cytokine milieu.[215] Although its immunologic consequences have not been fully elucidated, this circulating DNA likely contributes to tolerance and eventual exhaustion of antigen-specific CTLs. This phenomenon is well described for the human immunodeficiency virus, chronic

infection with which leads to progressive HIV-specific T cell dysfunction.[216] In addition to circulating nucleic acids, cellular fragments, known as *microparticles* or *exosomes*, can be detected in the peripheral blood of pregnant women in the third trimester.[217] Trophoblast-derived microparticles are proinflammatory, activate the coagulation system, can cause endothelial dysfunction, and are circulating at higher levels in pre-eclamptic vs normal pregnancies.[218] These microparticles are also involved in down-regulation of T-cell activity and deletion of activated T cells through interactions with FAS or TRAIL on the microparticle surface.[219] A similar phenomenon of cancer cell–derived microparticles contributing to the hypercoagulable state and impaired antitumor immunity of patients with cancer has been described (reviewed in Amin et al[220]). Microparticles derived from melanoma cells have been shown to express HLAG, likely contributing to their immunomodulatory properties.[221]

Just as circulating tumor cells have been identified in patients with early-stage malignancies,[222] intact trophoblast cells are also known to circulate in the maternal peripheral blood as early as the ninth week of pregnancy.[223] These fetally derived cells can engraft in the mother irrespective of HLA disparity and establish a long-term microchimerism that persists for decades after parturition.[224] Rates of fetal microchimerism are decreased in female patients with cancer (34%) compared with healthy controls (57%), and the immunomodulatory implications of this decrease are unclear.[225] An increased number of fetal microchimeric cells in aggressive breast carcinoma[226] and melanoma[227] during pregnancy have been observed. Whether these cells were recruited to the tumor microenvironment by inflammation and behave as innocent bystanders or whether they participate in tumor progression by providing angiogenic or tolerogenic signals is unclear at this time.

Many additional immunomodulatory proteins are secreted by trophoblast cells and can be found circulating in maternal peripheral blood. Among these molecules, soluble HLAG may be the most extensively studied.[228] Soluble HLAG impairs NK/DC cross-talk, promotes proinflammatory cytokine secretion from both uterine and peripheral blood mononuclear cells,[229] and induces apoptosis of $CD8^+$ cells through CD8 ligation[230] and FAS-FASL interaction.[231] Soluble HLAG has been well documented in malignancies,[174] including acute leukemia,[232] multiple myeloma,[233] lymphoproliferative disorders,[234] breast and ovarian carcinoma,[163] renal cell carcinoma,[165,235] lung cancer,[236] gliomas,[237] and melanoma.[238] Cancer cells can also trigger monocytes to release HLAG, further down-regulating antitumor immunity.[239] Whether HLAG can be targeted to break cancer-specific tolerance remains to be investigated.

A search for other immunomodulatory molecules from conditioned media of placental tissue has yielded interesting results. Surprisingly, no interleukins were identified by either proteomic analysis or sensitive radioimmunoassays; rather, in addition to pregnancy-associated hormones, substances including PSG1, glycodelin, TGF-β2, thrombospondin-1, PEDF, MIF, and galectin 1 were identified as important immunoregulators in pregnancy.[240] Many of these substances have been identified in cancer as well. For example, PSGs may not be pregnancy specific at all. Pregnancy-specific glycoprotein 9 deregulation is an early event in colorectal carcinogenesis.[241] Expressed frequently in lung carcinomas,[169] PSG1 is associated with estrogen receptor negativity and a higher risk of death in early-stage breast cancer.[242] Glycodelin may be involved in tumor angiogenesis by increasing VEGF release in many cell lines.[243] An inhibitor of TGF-β2 (overexpressed in many cancers) is in phase 1/2 cancer clinical trials.[13] Thrombospondin 1 is an endogenous angiogenesis inhibitor, although its expression in tumor stroma may render tumor cells insensitive to VEGF and help maintain tumor cell dormancy.[244] Another endogenous angiogenesis inhibitor, PEDF, may have anti-invasive effects on tumor cells.[245] MIF can stabilize HIF-1α, a factor central to cellular response to hypoxia.[246] Galectin1 expression within tumors and the stromal tissues is positively correlated with cancer aggressiveness[247] and a diminished T-cell response.[248]

Another soluble immunomodulator, soluble CD30, a member of the tumor necrosis superfamily of receptors and marker of T_H2 polarization, is increased in women with normal pregnancies and reduced in those with preeclampsia and intrauterine growth retardation.[249] In addition to being prognostic in patients with $CD30^+$ classical Hodgkin lymphoma,[250] soluble CD30 is a potential marker of chronic B cell hyperactivation and can predict those at risk of AIDS-associated non-Hodgkin lymphoma.[251] The identification of common immunomodulators helps expand the concept of tolerance in pregnancy and cancer beyond T_H2 and toward a more complete understanding of chronic inflammation, angiogenesis, and immunologic privilege.

IMPLICATIONS FOR CANCER THERAPEUTICS

As a healthy pregnancy progresses toward parturition, several changes within the mother reflect a restoration of active, T_H1-predominant immunity. Although T_{reg} levels stay constant until the postpartum period,[252] a gradual return of $CD16^+$ NK cells is observed in late pregnancy.[253] Suppressed earlier in pregnancy, circulating cytotoxic γδ-T cells increase with the onset of labor.[254] Interleukin 2 levels decrease while granulocyte macrophage colony–stimulating factor and interferon-γ increase through the third trimester and even more markedly at the onset of labor.[255] Increased expression of genes associated with acute

TABLE 2. **Immunomodulatory Genes Differentially Expressed in Melanoma vs Benign Melanocytic Lesions**[a]

Gene symbol	GSE4587 fold change (melanoma vs benign nevi)	*P* value	GSE3189[b] fold change (melanoma vs benign nevi)	*P* value
SPP1	77.4	<.001	20.3	<.001
IDO	34.7	<.001		
TIMP2	6.5	<.001	3.3	<.001
TLR2	6.0	<.001		
MMP9	5.9	.003	2.5	<.001
IL-8	5.8	.136	3.7	.007
TLR4	6.0	.018		
PTX3	4.4	.037		
MIF	4.1	.005	3.5	<.001
LGALS9	4.1	.002		
LGALS1	3.7	.004	4.1	<.001
LPL	1.4	.752	-3.2	<.001
FABP4	-2.2	.615	-2.3	.009
FZD10	-2.9	.168	-4.8	<.001

[a] IL-8 = interleukin 8. For expansion of all gene symbols, see Glossary to Genetics Terminology at the end of the article.
[b] GSE3189 used the Affymetrix HG-U133A GeneChip and therefore lacked some probes compared with the Affymetrix U133 Plus 2.0 array used by GSE4587.

inflammation and neutrophil and monocyte influx has been observed in human fetal membranes at parturition.[256,257] Concomitant with an increase in the potent uterine contractile prostanoid PGF-2α, proinflammatory cytokines and MMPs prepare the uterus for labor.[258] Markedly down-regulated at term compared with midgestation are genes involved in angiogenesis, such as angiopoietin 2.[259] Taken together, these changes support a transition from a T_H2 to a T_H1 polarity during the third trimester.

In contrast, patients with advanced malignancies continue to experience a progressive failure of antitumor immunity, which has been associated with a T_H2-polarization and VEGF-driven chronic inflammation.[260] We have identified the expression of immunomodulatory genes known to be supportive of pregnancy in our own patients with metastatic melanoma via gene-expression profiling (unpublished data). We have also verified that these immunomodulatory genes are differentially expressed in melanoma vs benign melanocytic nevi in 2 independent publically available datasets from the National Center for Biotechnology Information/GenBank GEO database: GSE4587,[261] which was analyzed on the GeneChip Human Genome U133 Plus 2.0 Array platform (Affymetrix, Santa Clara, CA), and GSE3189,[262] which was analyzed on the GeneChip Human Genome U133 Array Set HG-U133A platform (Affymetrix). We selected approximately 70 immunomodulatory genes on the basis of our critical review of the obstetrics literature, log-transformed the raw data, and performed an analysis of variance on this gene set on Partek 6.4 software. A summary of results is listed in Table 2. Osteopontin and other important components of innate immunity such as *TLR2* and *TLR4* and *PTX3* were significantly up-regulated in melanoma compared with benign nevi. Galectins 1 and 9 were also significantly up-regulated compared with nevi. Notably down-regulated in melanoma were genes known to be up-regulated in term placenta,[259,263] including *LPL*, *FABP4*, and *FZD10* (a Wnt receptor). Overall, this pattern is supportive of our theory that tumor cells use similar mechanisms of immune escape as those cells of the developing placenta, although these similarities have not yet been studied in a systematic fashion. Given what we have learned about the similarities between the placenta and tumor microenvironment, we plan to next comprehensively evaluate changes in systemic immune homeostasis in pregnancy vs cancer in order to prioritize potential therapeutic targets. In particular, identifying immunologic distinctions between pregnancy and cancer will be critical for this process.

CONCLUSION

By comparing immunologic patterns throughout healthy pregnancies, and in particular the return to T_H1-polarized immunity through the third trimester, with those patterns observed in advanced malignancies, we have an opportunity to learn potential mechanisms to overcome the burden of long-term antigenic exposure and immunologic exhaustion in patients with cancer. The challenge for investigators in this field will be to extend our observations beyond the T_H1/T_H2 paradigm in both pregnancy and cancer to a model that can both assess the status and guide treatment of malignancies in an individualized, rational, real-time manner. A critical need exists for the development of treatments aimed at all aspects of cancer: malignant proliferation, invasion, vasculogenic mimicry, angiogenesis, and immune privilege. Studying how all these aspects are orchestrated in the predictable, physiologic process of pregnancy can facilitate the search for novel cancer treatment strategies, from cytotoxic chemotherapy to biologic agents and immunologic adjuncts, in the often unpredictable and arduous fight against the pathologic process of cancer.

Glossary of Genetics Terminology

AKT = v-akt murine thymoma viral oncogene homolog
ALK = anaplastic lymphoma receptor tyrosine kinase
BCL2 = B cell chronic lymphocytic leukemia/lymphoma 2
CDK = cyclin dependent kinase
CEACAM1 = carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)
CMET (also known as *MET*) = met proto-oncogene (hepatocyte growth factor) receptor
CSF = colony-stimulating factor
CSF1R = CSF type 1 receptor
CXCR4 = chemokine (C-X-C motif) receptor 4

EGF = epidermal growth factor (beta-urogastrone)
ERK = extracellular signal–related kinase
FABP4 = fatty acid–binding protein 4
FAK = focal adhesion kinase
FAS = Fas (TNF receptor superfamily, member 6)
FASL = FAS ligand
FCγIIIA = FC gamma receptor III A
FGF = fibroblast growth factor
FLT1 = fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)
FOXP3 = forkhead box P3
FZD10 = frizzled homolog 10
GRO-α = growth-related oncogene α
HGF = hepatocyte growth factor
HIF-1α = hypoxia inducible factor 1α
HSP27 = heat shock protein 27
IDO = indoleamine 2, 3 dioxygenase
IGF = insulinlike growth factor
IGF1R = IGF type 1 receptor
ILT2 = Ig-like transcript 2
JAK = janus kinase
*LGALS*1 = galactin 1
*LGALS*9 = galactin 9
LPL = lipoprotein lipase
MAPK = mitogen-activated protein kinase
*MCP*1 = monocyte chemoattractant protein 1
MEK (also known as *MAP2K*) = MAPK/ERK kinase
MIF = macrophage migration inhibitory factor
Mig-7 = migration-induction protein 7
*MDM*2 = mouse double minute 2
MMP = matrix metalloproteinase
MTOR = mammalian target of rapamycin
MUC1 = mucin 1
NF-κB = nuclear factor κB
p38 = tumor protein 38
PAR1 = protease activated receptor 1
PDGF = platelet-derived growth factor
PDGFR = PDGF receptor
PEDF = pigment epithelial–derived factor
PGE2 = prostaglandin E2
PGF = placental growth factor
PI3K = phosphoinositide-3 kinase
PSG1 = pregnancy-specific glycoprotein 1
PTX3 = pentraxin 3
RANTES (also known as *CCL5*) = regulated on activation, normal T-cell expressed and secreted
RAF = v-raf-1 murine leukemia viral oncogene homolog 1
RAS = rat sarcoma viral oncogene homolog
SDF (also known as *CXCL12*) = stromal-derived factor 1
SPP1 = osteopontin
STAT = signal transducers and activator of transcription
TGF = transforming growth factor
TIM3 (also known as *HAVCR2*) = T cell immunoglobulin mucin 3
TIMP2 = tissue inhibitor of metalloproteinase 2
TLR = toll-like receptor
TNF = tumor necrosis factor
TRAIL = TNF-related apoptosis-inducing ligand
TRAILR = TRAIL receptor
uPA = urokinase plasminogen activator
VEGF = vascular endothelial growth factor
VEGFR = VEGF receptor
waf1/cip1 (also known as *CDKN1A*) = cyclin-dependent kinase inhibitor 1A
Wnt = wingless/T-cell factor
XIAP = X-link inhibitor of apoptosis protein

REFERENCES

1. Medawar PB. Some immunological and endocrinological problems raised by the evolution of viviparty in vertebrates. *Symp Soc Exp Biol*. 1953;7:320-338.

2. Clarke CA. Immunology of pregnancy: significance of blood group incompatibility between mother and foetus. *Proc R Soc Med*. 1968;61(11, pt 2):1213-1216.

3. Staun-Ram E, Shalev E. Human trophoblast function during the implantation process. *Reprod Biol Endocrinol*. 2005 Oct;3:56.

4. Lunghi L, Ferretti ME, Medici S, Biondi C, Vesce F. Control of human trophoblast function. *Reprod Biol Endocrinol*. 2007 Feb 8;5:6.

5. Fecher LA, Amaravadi RK, Flaherty KT. The MAPK pathway in melanoma. *Curr Opin Oncol*. 2008;20(2):183-189.

6. Ihle NT, Powis G. Take your PIK: phosphatidylinositol 3-kinase inhibitors race through the clinic and toward cancer therapy. *Mol Cancer Ther*. 2009;8(1):1-9.

7. Liu TJ, LaFortune T, Honda T, et al. Inhibition of both focal adhesion kinase and insulin-like growth factor-I receptor kinase suppresses glioma proliferation in vitro and in vivo. *Mol Cancer Ther*. 2007;6(4):1357-1367.

8. Martens T, Schmidt NO, Eckerich C, et al. A novel one-armed anti-c-Met antibody inhibits glioblastoma growth in vivo. *Clin Cancer Res*. 2006;12(20, pt 1):6144-6152.

9. Jun HT, Sun J, Rex K, et al. AMG 102, a fully human anti-hepatocyte growth factor/scatter factor neutralizing antibody, enhances the efficacy of temozolomide or docetaxel in U-87 MG cells and xenografts. *Clin Cancer Res*. 2007;13(22, pt 1):6735-6742.

10. García-Echeverría C, Pearson MA, Marti A, et al. In vivo antitumor activity of NVP-AEW541-A novel, potent, and selective inhibitor of the IGF-IR kinase. *Cancer Cell*. 2004;5(3):231-239.

11. Conway JG, McDonald B, Parham J, et al. Inhibition of colony-stimulating-factor-1 signaling in vivo with the orally bioavailable cFMS kinase inhibitor GW2580. *Proc Natl Acad Sci U S A*. 2005 Nov 1;102(44):16078-16083. Epub 2005 Oct 25.

12. Irvine KM, Burns CJ, Wilks AF, Su S, Hume DA, Sweet MJ. A CSF-1 receptor kinase inhibitor targets effector functions and inhibits pro-inflammatory cytokine production from murine macrophage populations. *FASEB J*. 2006 Sep;20(11):1921-1923. Epub 2006 Jul 28.

13. Schlingensiepen KH, Fischer-Blass B, Schmaus S, Ludwig S. Antisense therapeutics for tumor treatment: the TGF-beta2 inhibitor AP 12009 in clinical development against malignant tumors. *Recent Results Cancer Res*. 2008;177:137-150.

14. Yingling JM, Blanchard KL, Sawyer JS. Development of TGF-β signalling inhibitors for cancer therapy. *Nat Rev Drug Discov*. 2004;3(12):1011-1022.

15. Chen R, Wierda WG, Chubb S, et al. Mechanism of action of SNS-032, a novel cyclin-dependent kinase inhibitor, in chronic lymphocytic leukemia. *Blood*. 2009 May 7;113(19):4637-4645. Epub 2009 Feb 20.

16. Squires MS, Feltell RE, Wallis NG, et al. Biological characterization of AT7519, a small-molecule inhibitor of cyclin-dependent kinases, in human tumor cell lines. *Mol Cancer Ther*. 2009 Feb;8(2):324-332. Epub 2009 Jan 27.

17. Tojo M, Hamashima Y, Hanyu A, et al. The ALK-5 inhibitor A-83-01 inhibits Smad signaling and epithelial-to-mesenchymal transition by transforming growth factor-β. *Cancer Sci*. 2005;96(11):791-800.

18. Weroha SJ, Haluska P. IGF-1 receptor inhibitors in clinical trials--early lessons. *J Mammary Gland Biol Neoplasia*. 2008 Dec;13(4):471-483. Epub 2008 Nov 21.

19. Haluska P, Shaw HM, Batzel GN, et al. Phase I dose escalation study of the anti insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. *Clin Cancer Res*. 2007;13(19):5834-5840.

20. Lacy MQ, Alsina M, Fonseca R, et al. Phase I, pharmacokinetic and pharmacodynamic study of the anti-insulinlike growth factor type 1 Receptor monoclonal antibody CP-751,871 in patients with multiple myeloma. *J Clin Oncol*. 2008 Jul;26(19):3196-3203. Epub 2008 May 12.

21. Shen H, Moran DM, Maki CG. Transient nutlin-3a treatment promotes endoreduplication and the generation of therapy-resistant tetraploid cells. *Cancer Res*. 2008;68(20):8260-8268.

22. Gizatullin F, Yao Y, Kung V, Harding MW, Loda M, Shapiro GI. The Aurora kinase inhibitor VX-680 induces endoreduplication and apoptosis pref-

erentially in cells with compromised p53-dependent postmitotic checkpoint function. *Cancer Res*. 2006;66(15):7668-7677.

23. Prasad S, Kaur J, Roy P, Kalra N, Shukla Y. Theaflavins induce G2/M arrest by modulating expression of p21waf1/cip1, cdc25C and cyclin B in human prostate carcinoma PC-3 cells. *Life Sci*. 2007 Oct 13;81(17-18):1323-1331. Epub 2007 Sep 15.

24. Phase I study on monoclonal antibody TB-403 directed against PlGF in patients with solid tumours. ClinicalTrials.gov Web site. http://clinicaltrials.gov/ct2/show/NCT00702494. First received June 19, 2008. Last updated September 5, 2008. Accessed June 17, 2009.

25. Yodkeeree S, Chaiwangyen W, Garbisa S, Limtrakul P. Curcumin, demethoxycurcumin and bisdemethoxycurcumin differentially inhibit cancer cell invasion through the down-regulation of MMPs and uPA. *J Nutr Biochem*. 2009 Feb;20(2):87-95. Epub 2008 May 20.

26. Lee KJ, Hwang SJ, Choi JH, Jeong HG. Saponins derived from the roots of *Platycodon grandiflorum* inhibit HT-1080 cell invasion and MMPs activities: regulation of NF-κB activation via ROS signal pathway. *Cancer Lett*. 2008 Sep;268(2):233-243. Epub May 21.

27. Tuynman JB, Vermeulen L, Boon EM, et al. Cyclooxygenase-2 inhibition inhibits c-Met kinase activity and Wnt activity in colon cancer. *Cancer Res*. 2008;68(4):1213-1220.

28. Karp I, Behlouli H, Lelorier J, Pilote L. Statins and cancer risk. *Am J Med*. 2008;121(4):302-309.

29. Chiriva-Internati M, Grizzi F, Pinkston J, et al. Gamma-radiation upregulates MHC class I/II and ICAM-I molecules in multiple myeloma cell lines and primary tumors. *In Vitro Cell Dev Biol Anim*. 2006;42(3-4):89-95.

30. Chakraborty M, Wansley EK, Carrasquillo JA, et al. The use of chelated radionuclide (samarium-153-ethylenediaminetetramethylenephosphonate) to modulate phenotype of tumor cells and enhance T cell-mediated killing. *Clin Cancer Res*. 2008;14(13):4241-4249.

31. Adair SJ, Hogan KT. Treatment of ovarian cancer cell lines with 5-aza-2'-deoxycytidine upregulates the expression of cancer-testis antigens and class I major histocompatibility complex-encoded molecules. *Cancer Immunol Immunother.* 2009 Apr;58(4):589-601. Epub 2008 Sep 13.

32. Poláková K, Bandzuchová E, Kuba D, Russ G. Demethylating agent 5-aza-2'-deoxycytidine activates HLA-G expression in human leukemia cell lines. *Leuk Res.* 2009 Apr;33(4):518-524. Epub 2008 Sep 26.

33. Zweifel BS, Davis TW, Ornberg RL, Masferrer JL. Direct evidence for a role of cyclooxygenase 2-derived prostaglandin E2 in human head and neck xenograft tumors. *Cancer Res*. 2002;62(22):6706-6711.

34. Macor P, Tripodo C, Zorzet S, et al. In vivo targeting of human neutralizing antibodies against CD55 and CD59 to lymphoma cells increases the antitumor activity of rituximab. *Cancer Res*. 2007;67(21):10556-10563.

35. Basu GD, Tinder TL, Bradley JM, et al. Cyclooxygenase-2 inhibitor enhances the efficacy of a breast cancer vaccine: role of IDO. *J Immunol*. 2006;177(4):2391-2402.

36. Jia L, Schweikart K, Tomaszewski J, et al. Toxicology and pharmacokinetics of 1-methyl-d-tryptophan: absence of toxicity due to saturating absorption. *Food Chem Toxicol*. 2008 Jan;46(1):203-211. Epub 2007 Aug 10.

37. Charrad RS, Li Y, Delpech B, et al. Ligation of the CD44 adhesion molecule reverses blockage of differentiation in human acute myeloid leukemia. *Nat Med*. 1999;5(6):669-676.

38. Song EY, Qu CF, Rizvi SM, et al. Bismuth-213 radioimmunotherapy with C595 anti-MUC1 monoclonal antibody in an ovarian cancer ascites model. *Cancer Biol Ther*. 2008 Jan;7(1):76-80. Epub 2007 Oct 8.

39. Richman CM, Denardo SJ, O'Donnell RT, et al. High-dose radioimmunotherapy combined with fixed, low-dose paclitaxel in metastatic prostate and breast cancer by using a MUC-1 monoclonal antibody, m170, linked to indium-111/yttrium-90 via a cathepsin cleavable linker with cyclosporine to prevent human anti-mouse antibody. *Clin Cancer Res*. 2005;11(16):5920-5927.

40. Mac Gabhann F, Popel AS. Targeting neuropilin-1 to inhibit VEGF signaling in cancer: comparison of therapeutic approaches. *PLOS Comput Biol*. 2006 Dec 29;2(12):e180. Epub 2006 Nov 16.

41. Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. *Clin Cancer Res*. 2007 Jan;13(2, pt 2):709s-715s.

42. Verbrugge I, Wissink EH, Rooswinkel RW, et al. Combining radiotherapy with APO010 in cancer treatment. *Clin Cancer Res*. 2009 Mar 15;15(6):2031-2038. Epub 2009 Mar 10.

43. Dorgham K, Abadie V, Iga M, Hartley O, Gorochov G, Combadière B. Engineered CCR5 superagonist chemokine as adjuvant in anti-tumor DNA vaccination. *Vaccine*. 2008 Jun 19;26(26):3252-3260. Epub 2008 Apr 24.

44. Anderson DE. TIM-3 as a therapeutic target in human inflammatory diseases. *Expert Opin Ther Targets*. 2007;11(8):1005-1009.

45. Navabi H, Jasani B, Reece A, et al. A clinical grade poly I:C-analogue (Ampligen) promotes optimal DC maturation and Th1-type T cell responses of healthy donors and cancer patients in vitro. *Vaccine*. 2009 Jan 1;27(1):107-115. Epub 2008 Oct 31.

46. Prins RM, Craft N, Bruhn KW, et al. The TLR-7 agonist, imiquimod, enhances dendritic cell survival and promotes tumor antigen-specific T cell priming: relation to central nervous system antitumor immunity. *J Immunol*. 2006;176(1):157-164.

47. Chauhan D, Li G, Podar K, et al. A novel carbohydrate-based therapeutic GCS-100 overcomes bortezomib resistance and enhances dexamethasone-induced apoptosis in multiple myeloma cells. *Cancer Res*. 2005;65(18):8350-8358.

48. Delaine T, Cumpstey I, Ingrassia L, et al. Galectin-inhibitory thiodigalactoside ester derivatives have antimigratory effects in cultured lung and prostate cancer cells. *J Med Chem*. 2008;51(24):8109-8114.

49. Kretz-Rommel A, Qin F, Dakappagari N, Cofiell R, Faas SJ, Bowdish KS. Blockade of CD200 in the presence or absence of antibody effector function: implications for anti-CD200 therapy. *J Immunol*. 2008;180(92):699-705.

50. De Clercq E. Potential clinical applications of the CXCR4 antagonist bicyclam AMD3100. *Mini Rev Med Chem*. 2005;5(9):805-824.

51. Richert MM, Vaidya KS, Mills CN, et al. Inhibition of CXCR4 by CTCE-9908 inhibits breast cancer metastasis to lung and bone. *Oncol Rep*. 2009;21(3):761-767.

52. Gong M, Lu Z, Fang G, Bi J, Xue X. A small interfering RNA targeting osteopontin as gastric cancer therapeutics. *Cancer Lett.* 2008 Dec 8;272(1):148-159. Epub 2008 Aug 9.

53. Sekulic A, Haluska P Jr, Miller AJ, et al; Melanoma Study Group of Mayo Clinic Cancer Center. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin Proc*. 2008;83(7):825-846.

54. Bulmer JN, Morrison L, Johnson PM. Expression of the proliferation markers Ki67 and transferrin receptor by human trophoblast populations. *J Reprod Immunol*. 1988;14(3):291-302.

55. Kim NW, Piatyszek MA, Prowse KR, et al. Specific association of human telomerase activity with immortal cells and cancer. *Science*. 1994;266(5193):2011-2015.

56. Blagoev KB. Cell proliferation in the presence of telomerase. *PLoS One*. 2009;4(2):e4622. Epub 2009 Feb 27.

57. Kyo S, Takakura M, Tanaka M, et al. Expression of telomerase activity in human chorion. *Biochem Biophys Res Commun*. 1997;241(2):498-503.

58. Li F, Ambrosini G, Chu EY, et al. Control of apoptosis and mitotic spindle checkpoint by survivin. *Nature*. 1998;396(6711):580-584.

59. Lehner R, Bobak J, Kim NW, Shroyer AL, Shroyer KR. Localization of telomerase hTERT protein and survivin in placenta: relation to placental development and hydatidiform mole. *Obstet Gynecol*. 2001;97(6):965-970.

60. Fest S, Brachwitz N, Schumacher A, et al. Supporting the hypothesis of pregnancy as a tumor: survivin is upregulated in normal pregnant mice and participates in human trophoblast proliferation. *Am J Reprod Immunol*. 2008;59(1):75-83.

61. Shen J, Liu J, Long Y, et al. Knockdown of survivin expression by siRNAs enhances chemosensitivity of prostate cancer cells and attenuates its tumorigenicity. *Acta Biochim Biophys Sin (Shanghai)*. 2009;41(3):223-230.

62. Zhen HN, Li LW, Zhang W, et al. Short hairpin RNA targeting survivin inhibits growth and angiogenesis of glioma U251 cells. *Int J Oncol*. 2007;31(5):1111-1117.

63. Congmin G, Mu Z, Yihui M, Hanliang L. Survivin--an attractive target for RNAi in non-Hodgkin's lymphoma, Daudi cell line as a model. *Leuk Lymphoma*. 2006;47(9):1941-1948.

64. Li QX, Zhao J, Liu JY, et al. Survivin stable knockdown by siRNA inhibits tumor cell growth and angiogenesis in breast and cervical cancers. *Cancer Biol Ther*. 2006 Jul;5(7):860-866. Epub 2006 Jul 9.

65. Forbes K, Westwood M, Baker PN, Aplin JD. Insulin-like growth factor I and II regulate the life cycle of trophoblast in the developing human placenta. *Am J Physiol Cell Physiol*. 2008 Jun;294(6):C1313-C1322. Epub 2008 Apr 9.

66. Boldt HB, Conover CA. Pregnancy-associated plasma protein-A (PAPP-A): a local regulator of IGF bioavailability through cleavage of IGFBPs. *Growth Horm IGF Res*. 2007 Feb;17(1):10-18. Epub 2007 Jan 10.

67. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia [published correction appears in *Nat Rev Cancer.* 2009;9(3):224]. *Nat Rev Cancer*. 2008;8(12):915-928.

68. Tao Y, Pinzi V, Bourhis J, Deutsch E. Mechanisms of disease: signaling of the insulin-like growth factor 1 receptor pathway--therapeutic perspectives in cancer. *Nat Clin Pract Oncol*. 2007;4(10):591-602.

69. Hill DJ, Petrik J, Arany E. Growth factors and the regulation of fetal growth. *Diabetes Care*. 1998;21(suppl 2):B60-B69.

70. Papa V, Pezzino V, Costantino A, et al. Elevated insulin receptor content in human breast cancer. *J Clin Invest*. 1990;86(5):1503-1510.

71. Kalli KR, Conover CA. The insulin-like growth factor/insulin system in epithelial ovarian cancer. *Front Biosci*. 2003 May 1;8:d714-d722.

72. Marco DE, Cannas SA, Montemurro MA, Hu B, Cheng SY. Comparable ecological dynamics underlie early cancer invasion and species dispersal, involving self-organizing processes. *J Theor Biol*. 2009 Jan 7;256(1):65-75. Epub 2008 Oct 1.

73. Pollheimer J, Knöfler M. Signalling pathways regulating the invasive differentiation of human trophoblasts: a review. *Placenta.* 2005;26(suppl A): S21-S30.

74. Soundararajan R, Rao AJ. Trophoblast 'pseudo-tumorigenesis': significance and contributory factors. *Reprod Biol Endocrinol*. 2004 Mar 25;2:15. doi: 10.1186/1477-7827-2-15.

75. Ferretti C, Bruni L, Dangles-Marie V, Pecking AP, Bellet D. Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts. *Hum Reprod Update*. 2007 Mar-Apr;13(2):121-141. Epub 2006 Oct 26.

76. Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell*. 2008;14(6): 818-829.

77. Vicovac L, Aplin JD. Epithelial-mesenchymal transition during trophoblast differentiation. *Acta Anat (Basel)*. 1996;156(3):202-216.

78. Floridon C, Nielsen O, Holund B, et al. Localization of E-cadherin in villous, extravillous and vascular trophoblasts during intrauterine, ectopic and molar pregnancy. *Mol Hum Reprod*. 2000;6(10):943-950.

79. Blechschmidt K, Mylonas I, Mayr D, et al. Expression of E-cadherin and its repressor snail in placental tissue of normal, preeclamptic and HELLP pregnancies. *Virchows Arch*. 2007;450(2):195-202.

80. Matalon ST, Drucker L, Fishman A, Ornoy A, Lishner M. The role of heat shock protein 27 in extravillous trophoblast differentiation. *J Cell Biochem*. 2008;103(3):719-729.

81. Jäättelä M. Escaping cell death: survival proteins in cancer. *Exp Cell Res*. 1999;248(1):30-43.

82. Ciocca DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. *Cell Stress Chaperones*. 2005;10(2):86-103.

83. LaMarca HL, Dash PR, Vishnuthevan K, et al. Epidermal growth factor-stimulated extravillous cytotrophoblast motility is mediated by the activation of PI3-K, Akt and both p38 and p42/44 mitogen-activated protein kinases. *Hum Reprod*. 2008 Aug;23(8):1733-1741. Epub 2008 May 16.

84. Binker MG, Binker-Cosen AA, Richards D, Oliver B, Cosen-Binker LI. EGF promotes invasion by PANC-1 cells through Rac1/ROS-dependent secretion and activation of MMP-2. *Biochem Biophys Res Commun.* 2009 Feb 6; 379(2):445-450. Epub 2008 Dec 29.

85. Pollheimer J, Loregger T, Sonderegger S, et al. Activation of the canonical wingless/T-cell factor signaling pathway promotes invasive differentiation of human trophoblast. *Am J Pathol*. 2006;168(4):1134-1147.

86. Polakis P. The many ways of Wnt in cancer. *Curr Opin Genet Dev*. 2007; 17(1):45-51.

87. Xie H, Tranguch S, Jia X, et al. Inactivation of nuclear Wnt-β-catenin signaling limits blastocyst competency for implantation. *Development*. 2008 Feb;135(4):717-727. Epub 2008 Jan 16.

88. Grisaru-Granovsky S, Maoz M, Barzilay O, Yin YJ, Prus D, Bar-Shavit R. Protease activated receptor-1, PAR1, promotes placenta trophoblast invasion and β-catenin stabilization. *J Cell Physiol*. 2008;218(3):512-521.

89. Even-Ram SC, Grisaru-Granovsky S, Pruss D, et al. The pattern of expression of protease-activated receptors (PARs) during early trophoblast development. *J Pathol*. 2003;200(1):47-52.

90. Salah Z, Haupt S, Maoz M, et al. p53 controls hPar1 function and expression. *Oncogene*. 2008 Nov;27(54):6866-6874. Epub 2008 Sep 29.

91. Goerge T, Barg A, Schnaeker EM, et al. Tumor-derived matrix metalloproteinase-1 targets endothelial proteinase-activated receptor 1 promoting endothelial cell activation. *Cancer Res*. 2006;66(15):7766-7774.

92. Fitzgerald JS, Poehlmann TG, Schleussner E, Markert UR. Trophoblast invasion: the role of intracellular cytokine signalling via signal transducer and activator of transcription 3 (STAT3). *Hum Reprod Update*. 2008 Jul-Aug;14(4):335-344. Epub 2008 Apr 17.

93. Zybina TG, Frank HG, Biesterfeld S, Kaufmann P. Genome multiplication of extravillous trophoblast cells in human placenta in the course of differentiation and invasion into endometrium and myometrium: II, Mechanisms of polyploidization. *Tsitologiia*. 2004;46(7):640-648.

94. MacAuley A, Cross JC, Werb Z. Reprogramming the cell cycle for endoreduplication in rodent trophoblast cells. *Mol Biol Cell*. 1998;9(4): 795-807.

95. Lanzi C, Cassinelli G, Cuccuru G, et al. Cell cycle checkpoint efficiency and cellular response to paclitaxel in prostate cancer cells. *Prostate*. 2001; 48(4):254-264.

96. Puig PE, Guilly MN, Bouchot A, et al. Tumor cells can escape DNA-damaging cisplatin through DNA endoreduplication and reversible polyploidy. *Cell Biol Int.* 2008 Sep;32(9):1031-1043. Epub 2008 May 2.

97. Zhou Y, Fisher SJ, Janatpour M, et al. Human cytotrophoblasts adopt a vascular phenotype as they differentiate: a strategy for successful endovascular invasion? *J Clin Invest*. 1997;99(9):2139-2151.

98. Robertson GP. Mig-7 linked to vasculogenic mimicry. *Am J Pathol*. 2007; 170(5):1454-1456.

99. Maquoi E, van den Brûle FA, Castronovo V, Foidart JM. Changes in the distribution pattern of galectin-1 and galectin-3 in human placenta correlates with the differentiation pathways of trophoblasts. *Placenta*. 1997; 18(5-6):433-439.

100. Mourad-Zeidan AA, Melnikova VO, Wang H, Raz A, Bar-Eli M. Expression profiling of Galectin-3-depleted melanoma cells reveals its major role in melanoma cell plasticity and vasculogenic mimicry. *Am J Pathol*. 2008 Dec;173(6):1839-1852. Epub 2008 Nov 6.

101. Iurisci I, Cumashi A, Sherman AA, et al; Consorzio Interuniversitario Nazionale Per la Bio-Oncologia (Cinbo), Italy. Synthetic inhibitors of galectin-1 and -3 selectively modulate homotypic cell aggregation and tumor cell apoptosis. *Anticancer Res*. 2009;29(1):403-410.

102. Phillips TM, Lindsey JS. Carcinoma cell-specific Mig-7: a new potential marker for circulating and migrating cancer cells. *Oncol Rep*. 2005; 13(1):37-44.

103. Petty AP, Garman KL, Winn VD, Spidel CM, Lindsey JS. Overexpression of carcinoma and embryonic cytotrophoblast cell-specific Mig-7 induces invasion and vessel-like structure formation. *Am J Pathol*. 2007;170(5): 1763-1780.

104. van der Schaft DW, Seftor RE, Seftor EA, et al. Effects of angiogenesis inhibitors on vascular network formation by human endothelial and melanoma cells. *J Natl Cancer Inst*. 2004;96(19):1473-1477.

105. Condeelis J, Singer RH, Segall JE. The great escape: when cancer cells hijack the genes for chemotaxis and motility [published online ahead of print July 5, 2005]. *Annu Rev Cell Dev Biol*. 2005 Nov;21:695-718.

106. Schiessl B, Innes BA, Bulmer JN, et al. Localization of angiogenic growth factors and their receptors in the human placental bed throughout normal human pregnancy. *Placenta*. 2009 Jan;30(1):79-87. Epub 2008 Nov 17.

107. Cao Y, Liu Q. Therapeutic targets of multiple angiogenic factors for the treatment of cancer and metastasis. *Adv Cancer Res*. 2007;97:203-224.

108. Jain RK, Duda DG, Clark JW, Loeffler JS. Lessons from phase III clinical trials on anti-VEGF therapy for cancer. *Nat Clin Pract Oncol*. 2006; 3(1):24-40.

109. Shojaei F, Ferrara N. Role of the microenvironment in tumor growth and in refractoriness/resistance to anti-angiogenic therapies. *Drug Resist Updat*. 2008 Dec;11(6):219-230. Epub 2008 Oct 23.

110. Fischer C, Jonckx B, Mazzone M, et al. Anti-PlGF inhibits growth of VEGF(R)-inhibitor-resistant tumors without affecting healthy vessels. *Cell*. 2007;131(3):463-475.

111. Loges S, Roncal C, Carmeliet P. Development of targeted angiogenic medicine. *J Thromb Haemost.* 2009 Jan;7(1):21-33. Epub. 2008 Oct 25.

112. Shore VH, Wang TH, Wang CL, Torry RJ, Caudle MR, Torry DS. Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. *Placenta*. 1997;18(8):657-665.

113. Willett CG, Boucher Y, Duda DG, et al. Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients [letter]. *J Clin Oncol*. 2005;23(31):8136-8139.

114. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. *Cancer Cell*. 2007;12(1):9-22.

115. Wen HY, Abbasi S, Kellems RE, Xia Y. mTOR: a placental growth signaling sensor. *Placenta.* 2005;26(suppl A):S63-S69.

116. Roos S, Jansson N, Palmberg I, Säljö K, Powell TL, Jansson T. Mammalian target of rapamycin in the human placenta regulates leucine transport and is down-regulated in restricted fetal growth. *J Physiol*. 2007 Jul 1;582(pt 1): 449-459. Epub 2007 Apr 26.

117. Abraham RT, Eng CH. Mammalian target of rapamycin as a therapeutic target in oncology. *Expert Opin Ther Targets*. 2008;12(2):209-222.

118. Lane HA, Wood JM, McSheehy PM, et al. mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. *Clin Cancer Res*. 2009;15(5):1612-1622. Epub 2009 Feb 17.

119. Mor G. Pregnancy reconceived: what keeps a mother's immune system from treating her baby as foreign tissue? A new theory resolves the paradox. *Natural History.* May 1, 2007.

120. Moffett-King A. Natural killer cells and pregnancy [published correction appears in *Nat Rev Immunol.* 2002;2(12):975]. *Nat Rev Immunol*. 2002;2(9): 656-663.

121. Chiou SH, Sheu BC, Chang WC, Huang SC, Hong-Nerng H. Current concepts of tumor-infiltrating lymphocytes in human malignancies. *J Reprod Immunol*. 2005 Oct;67(1-2):35-50. Epub 2005 Aug 18.

122. Carlino C, Stabile H, Morrone S, et al. Recruitment of circulating NK cells through decidual tissues: a possible mechanism controlling NK cell accumulation in the uterus during early pregnancy. *Blood*. 2008 Mar 15; 111(6):3108-3115. Epub 2008 Jan 10.

123. Verma S, Hiby SE, Loke YW, King A. Human decidual natural killer cells express the receptor for and respond to the cytokine interleukin 15. *Biol Reprod*. 2000;62(4):959-968.

124. Keskin DB, Allan DS, Rybalov B, et al. TGFβ promotes conversion of CD16+ peripheral blood NK cells into CD16- NK cells with similarities to decidual NK cells. *Proc Natl Acad Sci U S A*. 2007 Feb;104(9):3378-3383. Epub 2007 Feb 20.

125. Koopman LA, Kopcow HD, Rybalov B, et al. Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. *J Exp Med*. 2003;198(8):1201-1212.

126. Hanna J, Goldman-Wohl D, Hamani Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. *Nat Med*. 2006 Sep;12(9):1065-1074. Epub 2006 Aug 6.

127. Saito S, Nakashima A, Myojo-Higuma S, Shiozaki A. The balance between cytotoxic NK cells and regulatory NK cells in human pregnancy. *J Reprod Immunol*. 2008 Jan;77(1):14-22. Epub 2007 Jun 11.

128. Wald O, Weiss ID, Wald H, et al. IFN-γ acts on T cells to induce NK cell mobilization and accumulation in target organs. *J Immunol*. 2006;176(8): 4716-4729.

129. Wittnebel S, Da Rocha S, Giron-Michel J, et al. Membrane-bound interleukin (IL)-15 on renal tumor cells rescues natural killer cells from IL-2 starvation-induced apoptosis. *Cancer Res*. 2007;67(12):5594-5599.

130. Carrega P, Morandi B, Costa R, et al. Natural killer cells infiltrating human nonsmall-cell lung cancer are enriched in CD56 bright CD16(-) cells and display an impaired capability to kill tumor cells. *Cancer*. 2008; 112(4):863-875.

131. Abumaree MH, Stone PR, Chamley LW. The effects of apoptotic, deported human placental trophoblast on macrophages: possible consequences for pregnancy. *J Reprod Immunol*. 2006;72(1-2):33-45. Epub 2006 Jul 14.

132. Gustafsson C, Mjösberg J, Matussek A, et al. Gene expression profiling of human decidual macrophages: evidence for immunosuppressive phenotype. *PLoS One*. 2008;3(4):e2078.

133. Hagemann T, Biswas SK, Lawrence T, Sica A, Lewis CE. Regulation of macrophage function in tumors: the multifaceted role of NF-κB. *Blood.* 2009 Apr 2;113(14):3139-3146. Epub 2009 Jan 26.

134. Hagemann T, Lawrence T, McNeish I, et al. "Re-educating" tumor-associated macrophages by targeting NF-κB. *J Exp Med*. 2008 Jun;205(6):1261-1268. Epub May 19.

135. Heikkinen J, Möttönen M, Alanen A, Lassila O. Phenotypic characterization of regulatory T cells in the human decidua. *Clin Exp Immunol*. 2004;136(2): 373-378.

136. Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology*. 2004;112(1):38-43.

137. Zhao JX, Zeng YY, Liu Y. Fetal alloantigen is responsible for the expansion of the CD4(+)CD25(+) regulatory T cell pool during pregnancy. *J Reprod Immunol*. 2007 Oct;75(2):71-81. Epub 2007 Aug 7.

138. Schumacher A, Wafula PO, Bertoja AZ, et al. Mechanisms of action of regulatory T cells specific for paternal antigens during pregnancy. *Obstet Gynecol*. 2007;110(5):1137-1145.

139. Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *Mol Hum Reprod*. 2004 May;10(5): 347-353. Epub 2004 Mar 2.

140. Steinborn A, Haensch GM, Mahnke K, et al. Distinct subsets of regulatory T cells during pregnancy: is the imbalance of these subsets involved in the pathogenesis of preeclampsia? *Clin Immunol*. 2008 Dec;129(3):401-412. Epub 2008 Sep 21.

141. Beyer M, Schultze JL. Regulatory T cells in cancer. *Blood*. 2006;108(3): 804-811.

142. Shen LS, Wang J, Shen DF, et al. CD4+CD25+CD127(low/-) regulatory T cells express Foxp3 and suppress effector T cell proliferation and contribute to gastric cancers progression. *Clin Immunol.* 2009 Apr;131(1):109-118. Epub 2009 Jan 18.

143. Giatromanolaki A, Bates GJ, Koukourakis MI, et al. The presence of tumor-infiltrating FOXP3+ lymphocytes correlates with intratumoral angiogenesis in endometrial cancer. *Gynecol Oncol*. 2008 Aug;110(2):216-221. Epub 2008 Jun 3.

144. Piersma SJ, Welters MJ, van der Burg SH. Tumor-specific regulatory T cells in cancer patients. *Hum Immunol*. 2008 Apr-May;69(4-5):241-249. Epub 2008 Mar 28.

145. Beyer M, Schultze JL. Immunoregulatory T cells: role and potential as a target in malignancy. *Curr Oncol Rep*. 2008;10(2):130-136.

146. Colombo MP, Piconese S. Regulatory-T-cell inhibition versus depletion: the right choice in cancer immunotherapy. *Nat Rev Cancer*. 2007;7(11): 880-887.

147. Zhang L, Dermawan KT, Jin ML, Xiong SD, Chu YW. Does chemotherapy augment anti-tumor immunotherapy by preferential impairment of regulatory T cells? *Med Hypotheses*. 2008 Nov;71(5):802-804. Epub 2008 Aug 8.

148. Miyazaki S, Tsuda H, Sakai M, et al. Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. *J Leukoc Biol*. 2003 Oct;74(4): 514-522. Epub 2003 Jul 15.

149. Kämmerer U, Schoppet M, McLellan AD, et al. Human decidua contains potent immunostimulatory CD83+ dendritic cells. *Am J Pathol*. 2000;157(1): 159-169.

150. Plaks V, Birnberg T, Berkutzki T, et al. Uterine DCs are crucial for decidua formation during embryo implantation in mice. *J Clin Invest*. 2008 Dec;118(12):3954-3965. Epub 2008 Nov 20.

151. Murdoch C, Muthana M, Coffelt SB, Lewis CE. The role of myeloid cells in the promotion of tumour angiogenesis. *Nat Rev Cancer*. 2008 Aug;8(8):618-631. Epub 2008 Jul 17.

152. Hunt JS, Orr HT. HLA and maternal-fetal recognition. *FASEB J*. 1992; 6(6):2344-2348.

153. Hunt JS, Andrews GK, Wood GW. Normal trophoblasts resist induction of class I HLA. *J Immunol*. 1987;138(8):2481-2487.

154. Campoli M, Ferrone S. HLA antigen changes in malignant cells: epigenetic mechanisms and biologic significance. *Oncogene*. 2008;27(45): 5869-5885.

155. Marchal JA, Boulaiz H, Rodriguez-Serrano F, et al. 5-fluorouracil derivatives induce differentiation mediated by tubulin and HLA class I modulation. *Med Chem*. 2007;3(3):233-239.

156. Fonsatti E, Nicolay HJ, Sigalotti L, et al. Functional up-regulation of human leukocyte antigen class I antigens expression by 5-aza-2'-deoxycytidine in cutaneous melanoma: immunotherapeutic implications. *Clin Cancer Res*. 2007;13(11):3333-3338.

157. McMaster MT, Librach CL, Zhou Y, et al. Human placental HLA-G expression is restricted to differentiated cytotrophoblasts. *J Immunol*. 1995;154(8):3771-3778.

158. Arnaiz-Villena A, Morales P, Gomez-Casado E, et al. Evolution of MHC-G in primates: a different kind of molecule for each group of species. *J Reprod Immunol*. 1999;43(2):111-125.

159. Hunt JS, Langat DK, McIntire RH, Morales PJ. The role of HLA-G in human pregnancy. *Reprod Biol Endocrinol*. 2006;4(suppl 1):S10.

160. Caumartin J, Favier B, Daouya M, et al. Trogocytosis-based generation of suppressive NK cells. *EMBO J*. 2007 Mar 7;26(5):1423-1433. Epub 2007 Feb 22.

161. Amiot L, Le Friec G, Sebti Y, et al. HLA-G and lymphoproliferative disorders. *Semin Cancer Biol*. 2003;13(5):379-385.

162. Bezuhly M, Howlett A, Colp P, et al. Quantitative HLA-G expression in metastasising and non-metastasising primary thin cutaneous melanomas [letter]. *Dermatology*. 2008;217(3):281-283. Epub 2008 Aug 7.

163. Kleinberg L, Flørenes VA, Skrede M, et al. Expression of HLA-G in malignant mesothelioma and clinically aggressive breast carcinoma. *Virchows Arch*. 2006 Jul;449(1):31-39. Epub 2006 Mar 16.

164. Davidson B, Elstrand MB, McMaster MT, et al. HLA-G expression in effusions is a possible marker of tumor susceptibility to chemotherapy in ovarian carcinoma. *Gynecol Oncol*. 2005;96(1):42-47.

165. Seliger B, Schlaf G. Structure, expression and function of HLA-G in renal cell carcinoma. *Semin Cancer Biol*. 2007;17(6):444-450. Epub 2007 Jul 13.

166. Yie SM, Yang H, Ye SR, Li K, Dong DD, Lin XM. Expression of HLA-G is associated with prognosis in esophageal squamous cell carcinoma. *Am J Clin Pathol*. 2007;128(6):1002-1009.

167. Yie SM, Yang H, Ye SR, Li K, Dong DD, Lin XM. Expression of human leukocyte antigen G (HLA-G) correlates with poor prognosis in gastric carcinoma. *Ann Surg Oncol*. 2007 Oct;14(10):2721-2729. Epub 2007 Jun 13.

168. Yoon BS, Kim YT, Kim JW, Kim SH, Kim JH, Kim SW. Expression of human leukocyte antigen-G and its correlation with interleukin-10 expression in cervical carcinoma. *Int J Gynaecol Obstet*. 2007Jul;98(1):48-53. Epub 2007 May 9.

169. Boucher LD, Yoneda K. The expression of trophoblastic cell markers by lung carcinomas. *Hum Pathol*. 1995;26(11):1201-1206.

170. El-Chennawi FA, Auf FA, El-Diasty AM, et al. Expression of HLA-G in cancer bladder. *Egypt J Immunol*. 2005;12(1):57-64.

171. Langat DK, Sue Platt J, Tawfik O, Fazleabas AT, Hunt JS. Differential expression of human leukocyte antigen-G (HLA-G) messenger RNAs and proteins in normal human prostate and prostatic adenocarcinoma. *J Reprod Immunol*. 2006 Aug;71(1):75-86. Epub 2006 Apr 17.

172. Barrier BF, Kendall BS, Sharpe-Timms KL, Kost ER. Characterization of human leukocyte antigen-G (HLA-G) expression in endometrial adenocarcinoma. *Gynecol Oncol*. 2006 Oct;103(1):25-30. Epub 2006 Mar 10.

173. Ye SR, Yang H, Li K, Dong DD, Lin XM, Yie SM. Human leukocyte antigen G expression: as a significant prognostic indicator for patients with colorectal cancer. *Mod Pathol*. 2007 Mar;20(3):375-383. Epub 2007 Feb 2.

174. Rebmann V, Regel J, Stolke D, Grosse-Wilde H. Secretion of sHLA-G molecules in malignancies. *Semin Cancer Biol*. 2003;13(5):371-377.

175. Yan WH, Lin A, Chen BG, et al. Unfavourable clinical implications for HLA-G expression in acute myeloid leukaemia. *J Cell Mol Med*. 2008;12(3): 889-898.
176. Veit TD, Chies JA. Tolerance versus immune response: MicroRNAs as important elements in the regulation of the HLA-G gene expression. *Transpl Immunol*. 2009 Mar;20(4):229-231. Epub 2008 Nov 25.
177. Onno M, Guillaudeux T, Amiot L, et al. The HLA-G gene is expressed at a low mRNA level in different human cells and tissues. *Hum Immunol*. 1994; 41(1):79-86.
178. Komohara Y, Harada M, Ishihara Y, et al. HLA-G as a target molecule in specific immunotherapy against renal cell carcinoma. *Oncol Rep*. 2007; 18(6):1463-1468.
179. Clark DA, Keil A, Chen Z, Markert U, Manuel J, Gorczynski RM. Placental trophoblast from successful human pregnancies expresses the tolerance signaling molecule, CD200 (OX-2). *Am J Reprod Immunol*. 2003; 50(3):187-195.
180. Moreaux J, Hose D, Reme T, et al. CD200 is a new prognostic factor in multiple myeloma [published correction appears in *Blood.* 2007;109(7):2717]. *Blood*. 2006 Dec 15;108(13):4194-4197. Epub 2006 Aug 31.
181. Tonks A, Hills R, White P, et al. CD200 as a prognostic factor in acute myeloid leukaemia [letter]. *Leukemia*. 2007 Mar;21(3):566-568. Epub 2007 Jan 25.
182. Siva A, Xin H, Qin F, Oltean D, Bowdish KS, Kretz-Rommel A. Immune modulation by melanoma and ovarian tumor cells through expression of the immunosuppressive molecule CD200. *Cancer Immunol Immunother*. 2008;57(7):987-996.
183. Kawasaki BT, Farrar WL. Cancer stem cells, CD200 and immunoevasion. *Trends Immunol*. 2008 Oct;29(10):464-468. Epub 2008 Sep 3.
184. Gray-Owen SD, Blumberg RS. CEACAM1: contact-dependent control of immunity. *Nat Rev Immunol*. 2006;6(6):433-446.
185. Briese J, Oberndörfer M, Pätschenik C, et al. Osteopontin is colocalized with the adhesion molecule CEACAM1 in the extravillous trophoblast of the human placenta and enhances invasion of CEACAM1-expressing placental cells. *J Clin Endocrinol Metab*. 2005 Sep;90(9):5407-5413. Epub 2005 Jun 14.
186. Dango S, Sienel W, Schreiber M, et al. Elevated expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) is associated with increased angiogenic potential in non-small-cell lung cancer. *Lung Cancer*. 2008 Jun;60(3):426-433. Epub 2008 Jan 22.
187. Thies A, Moll I, Berger J, et al. CEACAM1 expression in cutaneous malignant melanoma predicts the development of metastatic disease. *J Clin Oncol*. 2002;20:2530-2536.
188. Phillips TA, Ni J, Hunt JS. Death-inducing tumour necrosis factor (TNF) superfamily ligands and receptors are transcribed in human placentae, cytotrophoblasts, placental macrophages and placental cell lines. *Placenta*. 2001;22(8-9):663-672.
189. Phillips TA, Ni J, Pan G, et al. TRAIL (Apo-2L) and TRAIL receptors in human placentas: implications for immune privilege. *J Immunol*. 1999;162(10): 6053-6059.
190. Petroff MG, Chen L, Phillips TA, Azzola D, Sedlmayr P, Hunt JS. B7 family molecules are favorably positioned at the human maternal-fetal interface. *Biol Reprod*. 2003;68(5):1496-1504. Epub 2002 Nov 27.
191. van Mourik MS, Macklon NS, Heijnen CJ. Embryonic implantation: cytokines, adhesion molecules, and immune cells in establishing an implantation environment. *J Leukoc Biol.* 2009 Jan;85:4-19. Epub 2008 Sep 17.
192. Kao LC, Tulac S, Lobo S, et al. Global gene profiling in human endometrium during the window of implantation. *Endocrinology.* 2002;143(6):2119-2138.
193. Franchi A, Zaret J, Zhang X, Bocca S, Oehninger S. Expression of immunomodulatory genes, their protein products and specific ligands/receptors during the window of implantation in the human endometrium. *Mol Hum Reprod*. 2008;14(7):413-421.
194. Spendlove I, Ramage JM, Bradley R, Harris C, Durrant LG. Complement decay accelerating factor (DAF)/CD55 in cancer. *Cancer Immunol Immunother*. 2006;55(8):987-995.
195. Wang KX, Denhardt DT. Osteopontin: role in immune regulation and stress responses. *Cytokine Growth Factor Rev*. 2008;19(5-6):333-345.
196. Renkl AC, Wussler J, Ahrens T, et al. Osteopontin functionally activates dendritic cells and induces their differentiation toward a Th1-polarizing phenotype. Blood. 2005; 106(3):946-955.
197. Weber GF. Molecular mechanisms of metastasis. *Cancer Lett*. 2008;270(2):181-190.
198. Weber GF, Ashkar S, Cantor H. Interaction between CD44 and osteopontin as a potential basis for metastasis formation. *Proc Assoc Am Physicians*. 1997;109(1):1-9.
199. Fraccaroli L, Alfieri J, Larocca L, et al. A potential tolerogenic immune mechanism in a trophoblast cell line through the activation of chemokine-induced T cell death and regulatory T cell modulation. *Hum Reprod.* 2009 Jan;24(1): 166-175. Epub 2008 Sep 29.
200. Mellado M, de Ana AM, Moreno MC, Martínez C, Rodríguez-Frade JM. A potential immune escape mechanism by melanoma cells through the activation of chemokine-induced T cell death. *Curr Biol*. 2001;11(9):691-696.
201. Fest S, Aldo PB, Abrahams VM, et al. Trophoblast-macrophage interactions: a regulatory network for the protection of pregnancy. *Am J Reprod Immunol*. 2007;57(1):55-66.
202. Ancrile BB, O'Hayer KM, Counter CM. Oncogenic ras-induced expression of cytokines: a new target of anti-cancer therapeutics. *Mol Interv*. 2008;8(1):22-27.
203. Stathopoulos GT, Psallidas I, Moustaki A, et al. A central role for tumor-derived monocyte chemoattractant protein-1 in malignant pleural effusion. *J Natl Cancer Inst*. 2008 Oct 15;100(20):1464-1476. Epub 2008 Oct 7.
204. Koga M, Kai H, Egami K, et al. Mutant MCP-1 therapy inhibits tumor angiogenesis and growth of malignant melanoma in mice. *Biochem Biophys Res Commun*. 2008 Jan 11;365(2):279-284. Epub 2007 Nov 6.
205. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. *Clin Cancer Res*. 2008;14(21):6735-6741.
206. von Rango U, Krusche CA, Beier HM, Classen-Linke I. Indoleamine-dioxygenase is expressed in human decidua at the time maternal tolerance is established. *J Reprod Immunol*. 2007 Jun;74(1-2):34-45. Epub 2007 Feb 26.
207. Katz JB, Muller AJ, Prendergast GC. Indoleamine 2,3-dioxygenase in T-cell tolerance and tumoral immune escape. *Immunol Rev*. 2008 Apr; 222:206-221.
208. Schröcksnadel H, Baier-Bitterlich G, Dapunt O, Wachter H, Fuchs D. Decreased plasma tryptophan in pregnancy. *Obstet Gynecol*. 1996;88(1):47-50.
209. López AS, Alegre E, LeMaoult J, Carosella E, González A. Regulatory role of tryptophan degradation pathway in HLA-G expression by human monocyte-derived dendritic cells. *Mol Immunol*. 2006 Jul;43(14):2151-2160. Epub 2006 Feb 21.
210. von Bergwelt-Baildon MS, Popov A, Saric T, et al. CD25 and indoleamine 2,3-dioxygenase are up-regulated by prostaglandin E2 and expressed by tumor-associated dendritic cells in vivo: additional mechanisms of T-cell inhibition. *Blood*. 2006 Jul 1;108(1):228-237. Epub 2006 Mar 7.
211. Munn DH. Indoleamine 2,3-dioxygenase, tumor-induced tolerance and counter-regulation. *Curr Opin Immunol*. 2006 Apr;18(2):220-225. Epub 2006 Feb 7.
212. Sayama S, Yoshida R, Oku T, Imanishi J, Kishida T, Hayaishi O. Inhibition of interferon-mediated induction of indoleamine 2,3-dioxygenase in mouse lung by inhibitors of prostaglandin biosynthesis. *Proc Natl Acad Sci U S A*. 1981;78(12):7327-7330.
213. von Rango U. Fetal tolerance in human pregnancy--a crucial balance between acceptance and limitation of trophoblast invasion. *Immunol Lett*. 2008 Jan 15;115(1):21-32. Epub 2007 Nov 5.
214. Anker P, Mulcahy H, Chen XQ, Stroun M. Detection of circulating tumour DNA in the blood (plasma/serum) of cancer patients. *Cancer Metastasis Rev*. 1999;18(1):65-73.
215. Lo YM, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet*. 1997;350(9076):485-487.
216. Jones RB, Ndhlovu LC, Barbour JD, et al. Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection. *J Exp Med*. 2008 Nov;205(12):2763-2779. Epub 2008 Nov 10.
217. Taylor DD, Akyol S, Gercel-Taylor C. Pregnancy-associated exosomes and their modulation of T cell signaling. *J Immunol*. 2006;176(3): 1534-1542.
218. Redman CW, Sargent IL. Microparticles and immunomodulation in pregnancy and pre-eclampsia. *J Reprod Immunol*. 2007 Dec;76(1-2):61-67. Epub 2007 May 4.
219. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. *Nat Rev Immunol*. 2002;2(8):569-579.
220. Amin C, Mackman N, Key NS. Microparticles and cancer. *Pathophysiol Haemost Thromb*. 2008;36(3-4):177-183. Epub 2009 Jan 27.
221. Riteau B, Faure F, Menier C, et al. Exosomes bearing HLA-G are released by melanoma cells. *Hum Immunol*. 2003;64(11):1064-1072.
222. Alix-Panabières C, Riethdorf S, Pantel K. Circulating tumor cells and bone marrow micrometastasis. *Clin Cancer Res*. 2008;14(16):5013-5021.
223. Mueller UW, Hawes CS, Wright AE, et al. Isolation of fetal trophoblast cells from peripheral blood of pregnant women. *Lancet*. 1990; 336(8709):197-200.
224. Evans PC, Lambert N, Maloney S, Furst DE, Moore JM, Nelson JL. Long-term fetal microchimerism in peripheral blood mononuclear cell subsets in healthy women and women with scleroderma. *Blood*. 1999;93(6):2033-2037.
225. Gilmore GL, Haq B, Shadduck RK, Jasthy SL, Lister J. Fetal-maternal microchimerism in normal parous females and parous female cancer patients. *Exp Hematol*. 2008 Sep;36(9):1073-1077.
226. Dubernard G, Oster M, Chareyre F, et al. Increased fetal cell microchimerism in high grade breast carcinomas occurring during pregnancy. *Int J Cancer*. 2009;124(5):1054-1059.

227. Nguyen Huu S, Oster M, Avril MF, et al. Fetal microchimeric cells participate in tumour angiogenesis in melanomas occurring during pregnancy. *Am J Pathol*. 2009 Feb;174(2):630-637. Epub 2009 Jan 15.

228. Hunt JS, Jadhav L, Chu W, Geraghty DE, Ober C. Soluble HLA-G circulates in maternal blood during pregnancy. *Am J Obstet Gynecol*. 2000; 183(3):682-688.

229. van der Meer A, Lukassen HG, van Cranenbroek B, et al. Soluble HLA-G promotes Th1-type cytokine production by cytokine-activated uterine and peripheral natural killer cells. *Mol Hum Reprod*. 2007 Feb;13(2):123-133. Epub 2006 Nov 22.

230. Contini P, Ghio M, Poggi A, et al. Soluble HLA-A,-B,-C and -G molecules induce apoptosis in T and NK CD8+ cells and inhibit cytotoxic T cell activity through CD8 ligation. *Eur J Immunol*. 2003;33(1):125-134.

231. Puppo F, Contini P, Ghio M, Indiveri F. Soluble HLA class I molecules/CD8 ligation trigger apoptosis of CD8+ cells by Fas/Fas-ligand interaction. *Scientific World Journal*. 2002 Feb;2:421-423.

232. Gros F, Sebti Y, de Guibert S, et al. Soluble HLA-G molecules increase during acute leukemia, especially in subtypes affecting monocytic and lymphoid lineages. *Neoplasia*. 2006;8(3):223-230.

233. Leleu X, Le Friec G, Facon T, et al; Intergroupe Francophone du Myélome. Total soluble HLA class I and soluble HLA-G in multiple myeloma and monoclonal gammopathy of undetermined significance. *Clin Cancer Res*. 2005;11(20):7297-7303.

234. Sebti Y, Le Friec G, Pangault C, et al. Soluble HLA-G molecules are increased in lymphoproliferative disorders. *Hum Immunol*. 2003;64(11): 1093-1101.

235. Dunker K, Schlaf G, Bukur J, Altermann WW, Handke D, Seliger B. Expression and regulation of non-classical HLA-G in renal cell carcinoma. *Tissue Antigens*. 2008;72(2):137-148.

236. Urosevic M, Kurrer MO, Kamarashev J, et al. Human leukocyte antigen G up-regulation in lung cancer associates with high-grade histology, human leukocyte antigen class I loss and interleukin-10 production. *Am J Pathol*. 2001;159(3):817-824.

237. Wiendl H, Mitsdoerffer M, Hofmeister V, et al. A functional role of HLA-G expression in human gliomas: an alternative strategy of immune escape. *J Immunol*. 2002;168(9):4772-4780.

238. Ugurel S, Rebmann V, Ferrone S, Tilgen W, Grosse-Wilde H, Reinhold U. Soluble human leukocyte antigen--G serum level is elevated in melanoma patients and is further increased by interferon-α immunotherapy. *Cancer*. 2001;92(2):369-376.

239. Morandi F, Levreri I, Bocca P, et al. Human neuroblastoma cells trigger an immunosuppressive program in monocytes by stimulating soluble HLA-G release. *Cancer Res*. 2007;67(13):6433-6441.

240. Dong M, Ding G, Zhou J, Wang H, Zhao Y, Huang H. The effect of trophoblasts on T lymphocytes: possible regulatory effector molecules--a proteomic analysis. *Cell Physiol Biochem*. 2008;21(5-6):463-472. Epub 2008 Apr 24.

241. Salahshor S, Goncalves J, Chetty R, Gallinger S, Woodgett JR. Differential gene expression profile reveals deregulation of pregnancy specific beta1 glycoprotein 9 early during colorectal carcinogenesis. *BMC Cancer*. 2005 Jun 27;5:66.

242. Fagnart OC, Cambiaso CL, Lejeune MD, Noel G, Maisin H, Masson PL. Prognostic value of concentration of pregnancy-specific β_1-glycoprotein (SP1) in serum of patients with breast cancer. *Int J Cancer*. 1985;36(5):541-544.

243. Song M, Ramaswamy S, Ramachandran S, et al. Angiogenic role for glycodelin in tumorigenesis. *Proc Natl Acad Sci U S A*. 2001 Jul 31;98(16): 9265-9270. Epub 2001 Jul 17.

244. Kang SY, Watnick RS. Regulation of tumor dormancy as a function of tumor-mediated paracrine regulation of stromal Tsp-1 and VEGF expression. *APMIS*. 2008;116(7-8):638-647.

245. Fernandez-Garcia NI, Volpert OV, Jimenez B. Pigment epithelium-derived factor as a multifunctional antitumor factor. *J Mol Med*. 2007 Jan;85(1): 15-22. Epub 2006 Nov 15.

246. Rendon BE, Willer SS, Zundel W, Mitchell RA. Mechanisms of macrophage migration inhibitory factor (MIF)-dependent tumor microenvironmental adaptation. *Exp Mol Pathol.* 2009 Jun;86(3):180-185. Epub 2009 Jan 7.

247. Liu FT, Rabinovich GA. Galectins as modulators of tumour progression. *Nat Rev Cancer*. 2005;5(1):29-41.

248. Rabinovich GA, Liu FT, Hirashima M, Anderson A. An emerging role for galectins in tuning the immune response: lessons from experimental models of inflammatory disease, autoimmunity and cancer. *Scand J Immunol*. 2007;66(2-3):143-158.

249. Kusanovic JP, Romero R, Hassan SS, et al. Maternal serum soluble CD30 is increased in normal pregnancy, but decreased in preeclampsia and small for gestational age pregnancies. *J Matern Fetal Neonatal Med*. 2007; 20(12):867-878.

250. Casasnovas RO, Mounier N, Brice P, et al. Plasma cytokine and soluble receptor signature predicts outcome of patients with classical Hodgkin's lymphoma: a study from the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2007 May 1;25(13):1732-1740. Epub 2007 Mar 26.

251. Breen EC, Fatahi S, Epeldegui M, Boscardin WJ, Detels R, Martínez-Maza O. Elevated serum soluble CD30 precedes the development of AIDS-associated non-Hodgkin's B cell lymphoma. *Tumour Biol*. 2006;27(4):187-194. Epub 2006 Apr 27.

252. Saito S, Sasaki Y, Sakai M. $CD4^+CD25^{high}$ regulatory T cells in human pregnancy. *J Reprod Immunol*. 2005;65(2):111-120.

253. Rukavina D, Podack ER, Rubesa G, Spanjol-Pandelo S, Randic L. Down-regulated expression of perforin-positive/CD16+ cells in the peripheral blood lymphocytes in the first trimester of pregnancy and up-regulation at the end of pregnancy. *Am J Reprod Immunol*. 1997;38(3):189-196.

254. Barakonyi A, Miko E, Varga P, Szekeres-Bartho J. V-chain preference of gamma/delta T-cell receptors in peripheral blood during term labor. *Am J Reprod Immunol*. 2008;59(3):201-205.

255. Vassiliadis S, Ranella A, Papadimitriou L, Makrygiannakis A, Athanassakis I. Serum levels of pro- and anti-inflammatory cytokines in non-pregnant women, during pregnancy, labour and abortion. *Mediators Inflamm*. 1998;7(2):69-72.

256. Haddad R, Tromp G, Kuivaniemi H, et al. Human spontaneous labor without histologic chorioamnionitis is characterized by an acute inflammation gene expression signature. *Am J Obstet Gynecol.* 2006;195(2):394.e1-394.e24.

257. Bollopragada S, Youssef R, Jordan F, Greer I, Norman J, Nelson S. Term labor is associated with a core inflammatory response in human fetal membranes, myometrium, and cervix. *Am J Obstet Gynecol.* 2009;200(1):104. e1-104.e11.

258. Christiaens I, Zaragoza DB, Guilbert L, Robertson SA, Mitchell BF, Olson DM. Inflammatory processes in preterm and term parturition. *J Reprod Immunol*. 2008 Oct;79(1):50-57. Epub 2008 Jun 11.

259. Winn VD, Haimov-Kochman R, Paquet AC, et al. Gene expression profiling of the human maternal-fetal interface reveals dramatic changes between midgestation and term. *Endocrinology*. 2007 Mar;148(3):1059-1079. Epub 2006 Dec 14.

260. Nevala WK, Vachon CM, Leontovich AA, Scott CG, Thompson MA, Markovic SN; Melanoma Study Group of the Mayo Clinic Cancer Center. Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma. *Clin Cancer Res.* 2009 Mar 15;15(6):1931-1939. Epub 2009 Feb 24.

261. Smith AP, Hoek K, Becker D. Whole-genome expression profiling of the melanoma progression pathway reveals marked molecular differences between nevi/melanoma in situ and advanced-stage melanomas. *Cancer Biol Ther*. 2005 Sep;4(9):1018-1029. Epub 2005 Sep 9.

262. Talantov D, Mazumder A, Yu JX, et al. Novel genes associated with malignant melanoma but not benign melanocytic lesions. *Clin Cancer Res*. 2005; 11(20):7234-7242.

263. Mikheev AM, Nabekura T, Kaddoumi A, et al. Profiling gene expression in human placentae of different gestational ages: an OPRU Network and UW SCOR Study. *Reprod Sci*. 2008;15(9):866-877.